1995 WL 17831418 (Bd.Pat.App. & Interf.)

THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

Board of Patent Appeals and Interferences
Patent and Trademark Office (P.T.O.)

DAVID V. GOEDDEL AND SIDNEY PESTKA JUNIOR PARTY
[FN1]

v.

CHARLES WEISSMAN SENIOR PARTY
[FN2]

INTERFERENCE 101,601

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Final Hearing: March 2, 1992

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Sugano Exhibit 1018
Fiers v. Sugano
Interference 105,661

Before RONALD H. SMITH, DOWNEY and WILLIAM F. SMITH[FN3]
Administrative Patent Judges
DOWNEY
Administrative Patent Judge

This interference involves the application of Goeddel et al., Ser. No. 06/256,204 assigned to Genentech, Inc. and Hoffmann-LaRoche Inc.,[FN4] and the application of Weissmann, Ser. No. 06/471,301 assigned to Biogen N.V. c/o N.V. Fides.[FN5] The Goeddel et al. application claims benefit of their earlier filed U.S. applications, Ser. No. 205,578, filed November 10, 1980, Ser. No. 184,909, filed September 8, 1980, and Ser. No. 164,986, filed July 1, 1980. The Weissmann application claims benefit of his earlier filed U.S. application Ser. No. 223,108 filed January 1, 1981, UK application No. 8031737, filed Oct. 2, 1980, EPO application No. 80301100.6, filed April 3, 1980 and European Patent Office (EPO) application No. 80300079.3 filed January 8, 1980. In the declaration notice, party Weissmann was accorded benefit of the April 3, 1980 date of EPO 80301100.6 and thus

was made senior party.

The interference concerns certain mature human leukocyte interferon polypeptides. Human leukocyte interferons comprise a family of proteins that increase the resistance of cells to viral infection. The subject matter at issue is defined by a single count, which count is identical to claim 1 of the Goeddel et al. application. The count reads as follows:

COUNT 1

> A polypeptide of about 165-166 amino acids comprising the amino acid sequence of a mature human leukocyte interferon microbially produced and unaccompanied by any corresponding presequence or portion thereof.

Goeddel et al. claims 1-4, 8 and 52-69 and Weissmann claims 37-39, 41, 42, 77-79 and 85 and 87 correspond to the count.

During the preliminary motion stage of this proceeding, the parties filed numerous motions. However, only those motions raised by the parties in their briefs are dealt with herein.

The Examiner-in-Chief, hereinafter APJ[FN6], granted Weissmann motions (II.E.1, II.F and II.E.4) which added claims 77-79, 85 and 87 to his application to correspond to count 1 and which required Goeddel et al. to add claims 28, 30, 46-48, 50, 65, 67, 73, 75-78, 80-82, 85 and 86 to their application to correspond to count 1. On November 7, 1988, Goeddel et al. added the noted claims to their application as claims 52-69.[FN7]

***2** The APJ dismissed Goeddel et al. motions: (I.D.1) to add counts 2-4 to this interference and to be accorded benefit with respect thereto; (I.D.2) to add claims 28-40 to their application; and (I.D.3) to require Weissmann to add proposed claims "B" through "N" to his application. This decision was affirmed on reconsideration.

The APJ denied Goeddel et al. motions: (I.A.1 and I.A.2) to designate Weissmann claims 37-39, 41 and 42 and Goeddel et al. claims 4 and 8 as not corresponding to the count; (I.C.) for judgment on the grounds that Weissmann's claims 37-39, 41 and 42 are unpatentable to him under 35 USC 103; and (I.E.1 and I.E.2) to attack the benefit accorded Weissmann in the declaration notice of EPO application No. 80301100.6 filed April 3, 1980 and UK application No. 8031737, filed October 2, 1980. The APJ also denied Weissmann motion (II.C 1) to add counts 3-7 to the interference.

After the Weissmann testimony period closed, Goeddel et al. filed a second set of belated motions[FN8] attacking benefit accorded Weissmann of the April 3, 1980 EPO and October 2, 1980 UK applications for failure to disclose the best mode (Paper Nos. 199-201). Opposition papers were filed (Paper Nos. 211-212, accompanied by Exhibit 213) as were replies (Paper Nos. 222-223). These papers were deferred to final hearing.

Weissmann filed a belated motion (37 CFR §1.628) to amend paragraph 14 of his October 21, 1987 preliminary statement (Paper Nos. 170 and 171). An opposition and reply were filed (Paper Nos. 174 and 182, respectively).

Various motions to strike or suppress were filed by the parties.

The main briefs of the parties raise the following issues:

1. Is Goeddel et al. entitled to raise at final hearing the dispositions of I.D.1, I.D.2, I.D.3, II.E.1, and II.F, and if so, did the APJ properly dismiss I.D.1, I.D.2, I.D.3 and properly grant-in-part II.E.1, and II.F?
2. Goeddel et al. case for priority of invention.

3. Is Weissmann entitled to benefit of the April 3, 1980 and October 2, 1980 filing dates of his EPO and UK applications [I.E.1 and I.E.2]?
4. Did Goeddel et al. derive the invention from Weissmann?
5. Should Weissmann be allowed to amend his preliminary statement?
6. Did the APJ correctly deny the Weissmann motion to add counts 3-7 [II.C.1]?
7. Did the APJ correctly deny the Goeddel et al. motion for judgment [I.C]?
8. Did the APJ correctly deny the Goeddel et al. motion to redefine [I. A.1 and I.A.2]?
***3** 9. Goeddel et al. belated motions attacking benefit based on lack of best mode.

In addition, the following motions are before us:
10. Weissmann's belated motion to file a supplemental §1.682 notice accompanied by the supplemental notice and record (Paper Nos. 232, 233 and 234, Opposition Paper No. 239, Reply Paper No. 241).
11. The Goeddel et al. and Weissmann motions to suppress and strike:
a. Goeddel et al. motion to strike or deny consideration of portions of Weissmann's motion under 1.682 or to return the Weissmann motion as an unauthorized paper (Paper No. 246). An opposition and reply were filed, (Paper Nos. 240 and 248).
b. Weissmann motion to suppress the Weissbach Dep. Ex. 30 (Paper No. 244) Opposition (Paper No. 251).
c. Goeddel et al. motions to suppress the Bullock memo (Weissmann Exhibit Bullock 1) and Gould memo (Goeddel Weissbach Dep. Exhibit 33) (Paper No. 236) Opposition (Paper No. 245) and Reply (Paper No. 249).
d. Goeddel et al. motion to strike the first Gilbert declaration (Paper No. 237) Opposition (Paper No. 242) Reply (Paper No. 247).

The voluminous Goeddel et al. record includes the declaration and deposition testimony of Herbert Weissbach, David Goeddel, Philip Familletti, Russell McCandliss, Linda Randall, Elizabeth Yelverton, Laurie May, Kate Murashige, Parkash Jhurani, Thomas Dull, Grace Ju, Sidney Pestka, Alan Sloma, Herbert Boyer, Peter Lomedico, Jacques Van Boom, Menachem Rubinstein, Kenneth Berkowitz, George Gould, Jordan Gutterman, Josef Leiter, Brian McCarthy, Lee Simon and Richard Stevenson together with numerous exhibits. The voluminous Weissmann record includes the declaration and deposition testimony of Edward Bailey, Werner Boll, Francis Bullock, Joan Gallagher, Walter Gilbert, Alfred Goldberg, James Haley, Alan Hall, Masayoshi Mishina, Phillip Sharp, Charles Weissmann and Hal Wolkoff together with numerous exhibits.[FN9]

Both parties filed briefs and appeared through counsel at final hearing. The question of no interference-in-fact has not been raised.

Issue (1)

In their brief, Goeddel et al. raised the dismissal of their motions I.D.1, I.D.2 and I.D.3 and the granting-in-part of Weissmann motions II.E.1 and II.F.

During a conference call on March 4, 1989 (pursuant to 37 CFR §1.610(d)) between the APJ and lead counsel for the parties, counsel for Goeddel et al. stated that, in addition to priority, the only issues to be raised by party Goeddel et al. at final hearing would be the denial of motions I.E.1. and 2., I.C. and I.A.1. and 2. The APJ acknowledged the issues Goeddel et al. wished to raise at final hearing in his interlocutory order of April 5, 1989 (Paper No. 109). The APJ further indicated in that order that "No other testimony may be taken and no other is-

sues are entitled to be raised at final hearing."

***4** The purpose of a conference call is to simplify issues and to consider such matters as may aid in the disposition of an interference. In accordance with 37 CFR §1.2, the APJ's order represents the written record of the conference call and each party is expected to adhere to any agreement or commitment made during the call. Notwithstanding the APJ's order, Goeddel et al. assert that pursuant, to 37 CFR §§1.655(b) and (c), they are entitled to raise for consideration at final hearing the matters of I.D.1, I.D.2, I.D.3, II.E.1 and II.F because these matters were properly raised and the APJ improperly dismissed I.D.1, I.D.2, and I.D.3 and that such dismissal constitutes manifest error and/or an abuse of discretion or leads to manifest injustice.

Having stated that the only issues to be raised by them at final hearing would be the denial of the three above identified motions, Goeddel et al. waived their right to address matters presented either in their preliminary motions or oppositions to motions which were not raised by their opponent in its brief. To permit Goeddel et al. to do otherwise would vitiate the purpose of that procedure and be contrary to the spirit and purpose of the Rules, 37 CFR §1.601 et seq. If Goeddel et al. disagreed with any portion of the APJ's order, they could have, and in light of their subsequent actions should have, seasonably filed a request for modification within 14 days of the issuance of the order memorializing the conference call. No such request was filed.

An interlocutory order is presumed to have been correct. The Board may consider whether an interlocutory order is an abuse of discretion with the burden of showing such abuse being on the party attacking the order. 37 CFR §1.655(a).[FN10] By raising these matters now, Goeddel et al. is attacking the APJ's interlocutory order of April 5, 1989. However, they have not shown, nor do they allege, any abuse of discretion on the part of the APJ with respect to that order. Nor do we find any.

For the foregoing reasons, we decline to consider the questions raised in motions I.D.1, I.D.2., I.D.3., II.E.1. and II.F.

Issue (2)

The Goeddel et al. case for priority

Goeddel et al. presented a case for priority premised upon simultaneous conception and reduction to practice of the subject matter of the count on May 16, 1980. See GB 92-128, GR and exhibits cited therein. Weissmann does not challenge the Goeddel et al. priority case. See WB 2-3, II. Issues presented. In fact, Weissmann alleges that judgment should be awarded to him solely because he is entitled to the April 3, 1980 filing date of his EPO application and "Goeddel's date--May 16, 1980--is far too late." See WB 25, III. first full paragraph. Hence, Weissmann has conceded the date of May 16, 1980 to Goeddel et al. and we will now address whether Weissmann is entitled to the filing date of April 3, 1980.

Issue (3)

Is Weissmann entitled to benefit of the April 3, 1980 and October 2, 1980 filing dates of his earlier filed EPO and UK Applications[FN11]

A.

***5** Initially we point out that under the new rules, once an interference has been declared and a party seeks to change the status of the parties by motion, the moving party has the burden of persuasion to establish by a preponderance of the evidence that it is entitled to the relief sought. Kubota v. Shibuya, 999 F.2d 517, 519, n.2,

522, 27 USPQ2d 1418, 1420, n.2, 1422 (Fed. Cir. 1993). Hence, Goeddel et al. have the initial burden of establishing by a preponderance of the evidence that the Weissmann EPO application No. 80301100.6 filed April 3, 1980 [hereinafter April '80 EPO application] does not satisfy the enablement requirement of 35 USC 112, first paragraph, with respect to the count.[FN12]

Weissmann argues that since the APJ has twice found that the April '80 EPO application enables the count, first upon the declaration of the interference and second when the Goeddel et al. motion was denied, that pursuant to 37 CFR §1.655(a), Goeddel et al. bear the burden to show that these two decisions by the APJ were an abuse of discretion.

We reject this argument. The starting point for declaring an interference is form PTO-850 filled out by the primary examiner. Thus, contrary to Weissmann's allegation, the primary examiner, not the APJ, initially determined that Weissmann was entitled to benefit of an earlier filed application(s) with respect to the count. See Manual of Patent Examining Procedure, §2309.02. When an interference is declared, rebuttable presumptions are created which the parties may challenge by filing appropriate motions. Orikasa v. Oonishi, 10 USPQ2d 1996, 2005 (Comm'r. 1989). Subsequent events in an interference, such as the filing of a preliminary motion, may convince an APJ or a panel of the Board that an interference was not properly declared in the first instance. Here, the primary examiner accorded Weissmann benefit of April '80 EPO application on the PTO-850 and after the interference was declared, Goeddel et al. filed, inter alia, a preliminary motion to deny Weissmann benefit, 37 CFR §1.633(g). The APJ denied the Goeddel et al. motion. Since the parties have submitted additional testimony, evidence and arguments with respect to the issue of enablement making the record before us substantially different from that before the deciding APJ, we will not review the APJ's decision for an abuse of discretion, but rather we will decide whether the movant is entitled to the relief requested in view of the totality of evidence and arguments presented by the parties.

B.

We hold that the April '80 EPO application does not constitute a constructive reduction to practice of the invention of the count in that it fails to satisfy the enablement requirement of 35 USC 112, first paragraph. Accordingly, party Weissmann is not entitled to the benefit of April 3, 1980 filing date accorded it in the declaration notice.

***6** In their brief, Goeddel et al. argue that the April '80 EPO application does not enable the count because the application itself fails to describe or suggest a method of making a compound of the count and one skilled in the art using the extant state of art and the disclosure of the April '80 EPO application would not have been able to make a compound of the count without undue experimentation as of April 3, 1980. To support this position, Goeddel et al. rely principally upon the testimony of coinventor Goeddel (Dr. Goeddel), Professors Boyer and McCarthy. Goeddel et al. also rely upon the work performed by Drs. Mishina and Hall and Mr. Boll, coworkers of inventor Weissmann (Dr. Weissmann), after April 3, 1980 to demonstrate lack of enablement.

Contrarily, in his brief, Weissmann urges that the April '80 EPO application is enabled because a method of synthesis would have been obvious to one skilled in the art on April 3, 1980 from this application in combination with the Goeddel 1979 Nature article [hereinafter the Goeddel Nature article][FN13] and EPO application No. 1929 [hereinafter EPO 1929].[FN14] In support of this position, Weissmann relies upon the testimony of Dr. Weissmann, as well as that of Professors Gilbert, Sharp and Goldberg and the decision of Martin v. Johnson, 454 F.2d 746, 172 USPQ 391 (CCPA 1972) [An application is enabling even though it is "devoid of a disclosure

of how to make the compound" if "the method of synthesis would have been known to one of ordinary skill in the art."].

In order for a party to be accorded benefit of the filing date of an earlier application under 35 USC 119, the earlier application must satisfy the requirements of 35 USC 112, first paragraph, for an embodiment within the scope of the count, Bigham v. Godtfredsen, 857 F.2d 1415, 1417, 8 USPQ2d 1266, 1268 (Fed. Cir. 1988); Cross v. Iizuka, 753 F.2d 1040, 1043, 224 USPQ 739, 741 (Fed. Cir. 1985) and Kawai v. Metlesics, 480 F.2d 880, 891, 178 USPQ 158, 167 (CCPA 1973).

35 USC 112, first paragraph, provides in pertinent part:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...

The test of enablement is whether any person skilled in the art could make and use the invention from the disclosure in the application coupled with information known in the prior art without undue experimentation. Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986) cert. denied, 480 U.S. 947 (1987). Here enablement must be determined as of the April 3, 1980 filing date of the earlier filed EPO application. In re Wright, 999 F.2d 1557, 1563, 27 USPQ2d 1510, 1514 (Fed. Cir. 1993) [Events which occurred after filing date "are of no significance regarding what one skilled in the art believed as of that date." (footnote omitted)]. In re Glass, 492 F.2d 1228, 181 USPQ 31 (CCPA 1974). Each case must be considered on its own facts.

*7 The count is directed to certain polypeptide products that are defined in terms of the process by which they are produced.[FN15] The products are polypeptides of about 165-166 amino acids comprising the amino acid sequence of a mature human leukocyte interferon without any corresponding presequence or portion thereof. As stated, the products are microbially produced, for example in bacteria such as E. coli, using recombinant DNA technology. The count, as drafted, actually embraces a genus of mature human leukocyte interferons, and includes the species disclosed in the respective parties' applications, to wit, Weissmann's species <<alpha>>-1 and <<alpha>>-2, the Goeddel et al. species, LeIFA, LeIFB, LeIFC, LeIFD, LeIFE, LeIFG, LeIFH, LeIFI and LeIFJ, allelic variations thereof, either glycosylated or unglycosylated, all in either mature or methionylmature form.[FN16] The count excludes fusion proteins and precursor forms of human leukocyte interferon by the phrase "unaccompanied by any corresponding presequence or portion thereof."

The April '80 EPO application

The April '80 EPO application indicates that interferons in general protect cells against a wide spectrum of viruses. Disclosed are two species of human interferon, fibroblast (F) produced in diploid fibroblast and leukocyte (LeIf) produced together with minor amounts of (F) in human leukocyte and lymphoblastoid cells, both have been purified and characterized. Of interest here, LeIf contains two components, the first is 21,000-22,000 in molecular weight and the second is 15,000 to 18,000 in molecular weight which appears to represent the non-glycosylated form of the former. Interferons are not detectable in normal or healthy cells but are produced as a result of the cells' exposure to an interferon inducer. As of April 3, 1980, human leukocyte interferon was produced either through human cells grown in tissue culture or through human leukocytes collected from blood donors. In addition to its anti-viral action, the uses of human leukocyte interferon were wide ranging and these natural sources were not adequate to provide the needed quantities of human leukocyte interferon. Hence the discovery of alternative means for the production of human leukocyte interferon was desirable. See Background Art, pages 1-6.

The April '80 EPO application of Weissmann specifically describes a method for microbially producing a polypeptide which is trypsin sensitive, acid stable and has interferon-like activity.[FN17] Weissmann sequenced a DNA insert to a recombinant DNA molecule as set forth in Figures 8-10, determined the nucleotide bases representing the signal and mature sequences and deduced the amino acid sequence of the mature interferon therefrom. The polypeptide produced was sized and found to be "larger than authentic human leukocyte interferon, and the reason for that is almost certainly that it contains what is called a single [sic: signal] sequence." (Ju dec. Exh. 28, at B043522,[FN18] Weissbach Dep. Exh. 39, p. 116;[FN19] WR 1313)

***8** The April '80 EPO application claims, inter alia, a polypeptide having a deduced amino acid sequence for a mature human leukocyte interferon, a compound within the scope of the count. See footnote 12, supra.

Weissmann acknowledges that his April '80 EPO application does not describe a method of making a compound of the count. See Paper No. 42, p. 20, GR 10669 and WR 1370.[FN20] The issue here is whether the description of an amino acid sequence of a mature human leukocyte interferon coupled with prior art methods of heterologous gene expression would have enabled one skilled in the art as of April 3, 1980 to microbially produce mature human leukocyte interferon without undue experimentation.

The term "undue experimentation" does not appear in 35 USC 112 but it is well settled that enablement requires that the specification teach those in the art how to make and use the invention without undue experimentation. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing such factors as (i) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id., 858 F.2d at 737, 8 USPQ2d at 1404 citing Ex parte Forman, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986).

Weissmann states in the April '80 EPO application:

> [R]ecent advances in molecular biology have made it possible to introduce the DNA coding for specific nonbacterial eukaryotic proteins into bacterial cells. In general, with DNA other than that prepared via chemical synthesis, the construction of such recombinant DNA molecules comprises the steps of producing a single-stranded DNA copy (cDNA) of a purified messenger RNA (mRNA) template for the desired protein; converting the cDNA to double-stranded DNA; linking the DNA to an appropriate site in an appropriate cloning vehicle to form a recombinant DNA molecule and transforming an appropriate host with that recombinant DNA molecule. Such transformation may permit the host to produce the desired protein. (page 7, paragraph 1) (emphasis added)

Two publications which reflect these "recent advances" in this nascent technology are EPO 1929 and the Goeddel Nature article.

EPO 1929 is directed to the microbial production of human polypeptides, and in particular, somatostatin and insulin. Somatostatin, an inhibitor of the secretion of growth hormone, insulin and glucagon, is a polypeptide of 14 amino acids (page 6, lines 8-13). The process included chemically synthesizing a nucleotide sequence coding for the 14 amino acid polypeptide with an ATG start codon and fusing that sequence to the beta-galactosidase gene, placing the construct in an expression vector and transforming E. coli. The product was expressed as a fusion protein comprising a large portion of beta galactosidase and the met-somatostatin protein. This product was cleaved with cyanogen bromide at the methionine residue to release the active somatostatin protein product.

***9** With respect to insulin, a human polypeptide of 51 amino acids, the process is similar to that of somatostatin and involved chemically synthesizing (1) a nucleotide sequence coding for the 21 amino acid human insulin A chain and (2) a nucleotide sequence coding for the 30 amino acid human insulin B chain. A ATG start codon was positioned before the first codon of the nucleotide sequences coding for the respective chains. The two separate synthetic genes were fused to a beta galactosidase gene in a vector under the control of lac operon elements. E. coli were transformed with this construct. The products were expressed as individual fused proteins having a large number of amino acids of beta galactosidase fused to the respective A and B chains. Each of the fused polypeptides produced were partially purified, cleaved at their methionine residue with cyanogen bromide to release separate A and B chains which were then purified and recombined to form the 51 amino acid human insulin.

The Goeddel Nature article describes a process of microbially producing human growth hormone HGH, a protein of 191 amino acids in length, which is synthesized in the anterior lobe of the pituitary. Dr. Goeddel testified in regard to his HGH work that he turned to cDNA to obtain HGH because he did not find it feasible to chemically synthesize a protein of such large size. Dr. Goeddel also indicated that he did not want to produce a fusion protein since (1) such a fusion protein would not be pharmaceutically useful and (2) the HGH could not be released from the fusion protein using the prior art cyanogen bromide technique due to the number of internal methionine residues apart from the methionine resulting from the ATG start codon. (GR 403-404, 408-409).[FN21]

The Goeddel Nature article describes in great detail the hybrid cloning technique and expression of mature HGH as met-HGH. The article indicates that after first cloning the cDNA from human pituitary mRNA, sequencing the insert, and determining the restriction endonuclease pattern, a double stranded HGH cDNA was treated with HaeIII giving a DNA fragment of 551 base pairs which included coding sequences for amino acids 23-191+ of HGH. To complete the needed nucleotide sequence, a DNA adaptor fragment containing an ATG initiation codon and coding sequences for residues 1-23 of HGH was chemically synthesized. The two fragments were separately cloned and then combined to form a synthetic-natural 'hybrid' gene which was then modified with appropriate ends in order to ligate it to a prepared plasmid. The prepared plasmid was modified to contain tandem lac UV-5 promoters and appropriate ends to accept the 'hybrid'. In addition, the promoter sequence of the tc^R gene and distal EcoRI were removed from the plasmid. The synthetic-natural 'hybrid' gene was ligated into the prepared plasmid and positioned with respect to the promoter and ATG codon. This construct was then transformed into various E. coli extracts. See Table 1. The plan to express HGH included positioning two base pairs between the EcoRI sticky end and the ATG initiation codon such that the lac AGGA ribosome binding site was eleven (11) base pairs from the ATG translational start for HGH. Other prepared plasmids positioned the ribosome site seven (7) base pairs from the ATG start codon. The Goeddel Nature article, at page 548, states that

> ***10** This is the first time that a human polypeptide has been directly expressed in E.coli in a non-precursor form.. The hybrid DNA cloning techniques described as a route to the cloning and expression of HGH coding sequences in E.coli are generally applicable to other polypeptides which are synthesized initially as inactive precursors and later processed, or for which full length cDNA transcripts are unavailable. (emphasis added)

We hold that Goeddel et al. have sustained their burden of proof to establish by a preponderance of the evidence that the April '80 EPO application of Weissmann is not enabling with respect to making a compound of the count. As admitted by Weissmann, his April '80 EPO application does not disclose any method for making a compound of the count. Nor does it direct one skilled in the art to other prior art disclosures for the needed information. As of April 3, 1980, the prior art did not disclose even in general terms how to microbially produce mature or met-mature human leukocyte interferon.

As is clear from the April '80 EPO application, as of April 1980, the ability of workers to express human proteins in bacteria was a very recent advance in molecular biology, i.e., the field was in its infancy. At that time, researchers were not directly expressing heterologous genes in bacteria in a routine manner. As explained by Boyer, as of April 3, 1980, researchers in the art of molecular biology were seriously concerned that attempts to produce specific mature mammalian proteins in bacteria would be fraught with problems since bacteria simply do not ordinarily produce mammalian or other eukaryotic proteins and there are major differences that render efforts to express specific mammalian proteins in bacteria unpredictable. (GR 2069-2077, ¶¶ 39-50). Boyer lists a number of concerns (GR 2070-2071) in expressing mammalian proteins in E. coli, including (1) instability of the mammalian gene and the recombinant expression vector containing it in the bacteria cell, (2) inability of the bacterial cell to transcribe the mammalian gene, (3) instability of mRNA encoding the mammalian protein in the bacterial cell, (4) inability of bacteria to translate the mammalian mRNA into protein, (5) instability of the mammalian protein in the bacteria environment, (6) inability of the bacterial cell to fold the mammalian protein into its proper three-dimensional conformation; and (7) instability of the biological activity of the bacterially-produced mammalian protein. (See also GB 83-86). Boyer testified that these concerns "would lead one to say that you couldn't predict with any degree of certainty that any construct is going to make a particular protein." (GR 2184). Unpredictability of an art area alone can lead to a conclusion of nonenablement. In re Marzocchi, 439 F.2d 220, 169 USPQ 367 (CCPA 1971); In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970).

***11** In rebuttal, Weissmann urges that the Goeddel Nature article and EPO 1929, especially as interpreted by Genentech in its paper filed December 20, 1990 in an opposition proceeding in the European Patent Office, provide the necessary information to make a compound of the count. We disagree. We find it significant that these two publications were in fact disclosed in the April '80 EPO application, yet the April '80 EPO application, while describing the deduced amino acid sequence of the mature human leukocyte interferon, does not state that the techniques described in these two publications would be useful for the production of human leukocyte interferon. To the contrary, Weissmann stated in the April '80 EPO application that "[N]one of the foregoing [publications] however is directed, as is this invention, toward the synthesis of HIF with use of recombinant DNA technology."

The contemporaneous statements made in the April '80 EPO application by Weissmann are relevant evidence establishing that Weissmann did not think, as of April 3, 1980, that these two publications were at all significant or relevant to the production of human leukocyte interferon in contrast to his position in this interference. In our view those contemporaneous statements are entitled to significantly more weight than Weissman's belated reliance upon these two documents after this interference was declared. Thus on its face, the April '80 EPO application does not provide any guidance with respect to the direction one should proceed to produce a compound of the count. In fact, by distancing itself from the two publications Weissmann now relies upon, the April '80 EPO application can reasonably be read as directly teaching away from the procedure Weissmann now argues would have been applicable.

Weissmann points to the prophetic statement made at page 548 of the Goeddel Nature article and alleges that it provides a reasonable basis to conclude that that method is applicable to the microbial production of other polypeptides initially made in precursor form, such as interferon. We do not read "generally applicable" as the phrase is used in this prophetic statement to mean that at that embryonic stage of this art that novel hybrid cloning technique would necessarily work with any other specific protein.

In fact, Dr. Goeddel testified that it was not possible to use the Goeddel Nature article method to tailor the DNA fragment for fibroblast (beta) interferon. (GR 315-316 ¶35). Rather, Dr. Goeddel needed to develop another

method for the production of DNA construct of fibroblast (beta) interferon.[FN22] Weissmann himself, when questioned about the Goeddel Nature article and the usefulness of the Goeddel techniques for proteins other than HGH, said "...the methods described in this paper are generally applicable to other polypeptides which are synthesized as inactive precursors and later process [sic, processed]" (emphasis added) (WR 1122). Boyer, referring also to the Goeddel Nature article, indicated that as far as the HGH method was concerned, there were two things to consider, the first was the "general applicability" in terms of making a construct and the second was whether or not one can predict whether one could successfully produce a protein from the construct (GR 2155). Boyer further stated in respect to the HGH method that "one can go ahead and try it, there is no guarantee it will work." (GR 2159) and that "the uncertainty was whether or not one could have the construct make the appropriate protein." (GR 2159). Weissbach testified that the HGH information "was but a starting place to try to express a protein, one could not be sure whether it would work." When questioned why, Weissbach explained that it was a complicated process which depended in large part on the sequence of the protein. Each protein is different and one could not be sure that one could use this procedure to construct a proper high expression clone. In addition, there are many other steps involved between the time a clone is obtained and actual synthesis of the protein by an organism. (See GR 191-192). Dr. Goeddel himself stated that having the sequence and HGH method is not enough, i.e., that only with that information is it possible to design a method to try to directly express. The information shown in the Goeddel Nature article does not tell you how to "do interferon." (See GR 454-455).

***12** Weissmann also relies upon the opinion testimony of Professors Gilbert and Sharp (Gilbert and Sharp) (WR 268-272 and 822-829) to show that, as of April 3, 1980, a person skilled in the art could have been able to produce a mature human leukocyte compound of the count having knowledge of the April '80 EPO application containing the method of producing a polypeptide having interferon activity, the nucleotide sequence of Dr. Weissmann's cDNA and the identity of the first codon of mature human leukocyte interferon of that DNA sequence, combined with the technique for expressing a mature form of a polypeptide disclosed in the Goeddel Nature article. Gilbert and Sharp set forth the following steps:

(a) make and isolate a cDNA encoding pre-human leukocyte interferon;

(b) determine the DNA sequence of that cDNA and locate the N-terminal of the mature human leukocyte interferon coded for it;

(c) restrict that cDNA with a restriction endonuclease that cuts in the N-terminal portion of the coding region for mature human leukocyte interferon;

(d) synthesize a DNA linker having, in the 5' to 3' direction:

(i) an ATG codon, and

(ii) the excised portion of the mature human leukocyte interferon cDNA;

(e) ligate the synthetic linker and the restricted cDNA into a microbial expression vector at an appropriate position for expression; and

(f) transform an appropriate microbial host with the expression vector containing the synthetic DNA-cDNA hybrid and culturing that host.

With respect to these various steps, Gilbert and Sharp indicate that steps (a) and (b) are found in the April '80 EPO application. As to step (c), they indicate that restriction endonucleases, their sites and methods for restricting DNA with them were well known in February 1980. They specifically refer to the use of DpnII (MboI) (or Sau3A), DdeI or AvaII, all of which have recognition sequences within the N-terminal portion of the mature coding sequence of human leukocyte interferon as of April 3, 1980. For step (d), linkers could be ordered and purchased at this time. As to steps (e) and (f), Gilbert and Sharp assert that ligation, transformation and culturing were "standard and highly predictable techniques in the field of genetic engineering" in February 1980. Specific

examples of these techniques were described by Dr. Weissmann at the Martinique meeting and the MIT seminar, in the Nagata Nature paper ...and in the April 1980 EPO application."

While these individual steps and techniques may have been known at that time, in view of the embryonic nature of this field and the lack of guidance in the specification, it is difficult to find a reasonable basis to conclude that one would have obtained expression of the protein by these techniques without further guidance as to the direction that experimentation should take. While we recognize that a production specification is not required to satisfy the enablement requirement of 35 USC 112, first paragraph, the purpose of this section of the statute is to make an invention fully available to the public without any requirement of undue experimentation. Cf. Martin v. Johnson, supra, wherein a organic chemist provided a detailed explanation of how a person skilled in the art would have prepared 3-(p-bromo-phenyl)-1-methyl-1-methoxyurea by using p-bromophenyl isocyanate as a reactant instead of p-chlorophenyl isocyanate in the reaction of p-chlorophenyl isocyanate with O,N-dimethyl hydroxylamine in benzene. Here, experimentation is needed to determine at a minimum appropriate ligation sites, appropriate cloning molecules to form the recombinant DNA molecule, appropriate hosts, etc. As noted by Weissmann himself in the April '80 EPO application, even if one fortuitously selects appropriate materials, expression is not guaranteed, only that with appropriate selections "transformation may permit the host to express." See the April '80 EPO application at page 7, lines 12-13. Boyer stated that "every protein had its own series of problems relating to expression."(GR 2165). Hence, we conclude that the Gilbert and Sharp testimony does not establish that one skilled in the art would have been able to practice the count without undue experimentation.

***13** Weissmann would also have us look to the April '80 EPO application and its 55 pages of examples disclosing "how to produce biologically active interferon microbially." This argument is not relevant in that the product which is actually produced in the application is not a compound within the scope of the count.

Weissmann directs us to the Goeddel Nature article to show detailed, actual examples of making a mature form of HGH.[FN23] However, Dr. Goeddel when questioned with respect to the lack of activity in a radioimmunoassay of somatostatin, postured that the most likely reasons for the inability to detect protein are no synthesis of the protein or very rapid degradation. (GR 390).

Weissmann further directs our attention to the Goeddel et al. patent application on HGH filed in 1979 and issued as U.S. Pat. No. 4,343,832 on August 3, 1982 (WR 9730-9742) for a teaching that the method of the Goeddel Nature article was particularly useful for the production of mature interferon. This patent cannot be used to show the state of the art as of the April 3, 1980 filing date since it issued thereafter and thus it is inappropriate for us to consider it. In re Glass, 492 F.2d at 1231, 181 USPQ at 34 [A patent may be available as prior art under 35 USC 102(e), however it does not show what is known generally to any person skilled in the art as of its filing date.]

Weissmann also directs us to the Swanson and Leibowitz statements, found in the Gould memo (WX Sharp 14) and the Bullock memo (WX Bullock 1), respectively, alleging that these statements also establish that the method in the Goeddel Nature article is applicable to interferon. Weissmann relies upon the following statement attributed to Swanson, president of Genentech, that "they had an exciting breakthrough regarding human growth hormone production by recombinant-DNA techniques which they believe would be applicable to the interferon project." The Swanson statement, in our view, does not reflect what one skilled in the art knew at the time of filing of the April '80 EPO application. Moreover, these statements indicate no more than the prophetic statement contained in the Goeddel Nature article that technique is generally applicable to other polypeptides. The Bullock

memo is not before us.[FN24]

Weissmann has also proffered the Genentech paper (WR 111747-11781) dated December 20, 1990 and filed in an EPO opposition proceeding involving EPO 1929, alleging that in that paper, Genentech, the Goeddel et al. coassignee, interprets EPO 1929 to describe microbial production of human proteins "as such" unfused to any other protein. WB 15-16, 32. We give little weight to this evidence since the statements made by Genentech in 1990 are not revelant to what one skilled in the art believed as of April 3, 1980. Moreover, we do not find any basis upon which to conclude that the EPO 1929 application teaches one of ordinary skill in the art how to express heterologous genes in bacteria without a presequence since the disclosure and examples therein are all directed to the production of fusion proteins which are later cleaved to release the mature protein.

***14** We are not persuaded by the allegations of Weissmann's witnesses that all of the concerns iterated by Boyer relating to stability and degradation dissipate simply because the April '80 EPO application describes microbial production of a polypeptide having interferon activity. That polypeptide product is not within the scope of the count and the Weissmann witnesses have not presented a proper factual basis, only opinion, to conclude that one skilled in the art would have successfully extrapolated the April '80 EPO application technique for producing a polypeptide having interferon activity to producing the mature human leukocyte interferon of the count. Moreover, stability is a nonissue unless protein expression occurs. In addition, the Goldberg opinion of the Taniguchi et al. article[FN25] appears, in our view, to be inconsistent with his position that one of ordinary skill realized that smaller proteins are less stable than large mammalian proteins. EPO 1929 indicates that size is relevant to survival. Taniguchi et al. shows that both the larger preprotein and smaller mature fibroblast protein degrade. Both EPO 1929 and the Goeddel Nature article evince degradation concerns with their respective proteins. Further, Weissbach testified that stability was a definite concern in this new area of research because people were not expressing eukaroytic proteins in bacteria (GR 261-262) and that one could not predict degradation (GR 263). This is further evidence of the uncertainty as to whether microbial expression of interferon as of April 3, 1980 would have been successful.[FN26]

In holding that Goeddel et al. sustained their burden and that the Weissmann evidence is not an adequate rebuttal, it should be noted that we give little weight to the work done by Drs. Mishina and Boll and Mr. Hall, coworkers of Dr. Weissmann, after the filing date of the April 3, 1980. Goeddel et al. urge that this evidence shows that a number of attempts were unsuccessful, that Weissmann was not able to produce a mature interferon of the count until October 21, 1980 and that even this successful attempt did not use the exact procedure of the Goeddel Nature article but, rather, Dr. Weissmann used a variant thereof.[FN27] Goeddel et al. argue that this evidence establishes nonenablement as of April 3, 1980, that is, one skilled in the art would not have been able to use the Goeddel et al. Nature article procedures to produce mature human leukocyte interferon as it was used to produce HGH without undue experimentation. Not surprisingly, Weissmann relies upon this same work as evidence that he successfully microbially produced a compound within the scope of the count by October 21, 1980. We have given this evidence little weight in reaching this decision since it is of little, if any, relevance to the question of enablement. Neither party has established that these developments which occurred after the effective filing date of the April '80 EPO application are of significance in determining what one skilled in the art believed as of that date. Enablement is determined as of the April 3, 1980 filing date of the patent application. In re Wright, supra; In re Glass, supra.

***15** For the above reasons, we find that Goeddel et al. have sustained their burden and Weissmann's rebuttal is ineffective.

Issue (4)

Did Goeddel et al. derive the invention of the count from Weissmann

Since Weissmann is not entitled to benefit of the April 3, 1980 filing date, the only way that Weissmann may prevail is to prove derivation. We hold that Goeddel et al. did not derive the invention of the count from Weissmann by April 15, 1980 as alleged by Weissmann.

The party charging derivation has the burden of showing prior complete conception of the subject matter of the count and sufficient communication of the subject matter to the party charged to enable one of ordinary skill in the art to construct and successfully operate the invention. Mead v. McKirnan, 585 F.2d 504, 507, 199 USPQ 513, 515 (CCPA 1978). Conception is "the formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." Hybritech, supra, 802 F.2d at 1376, 231 USPQ at 87. Conception is complete only when the idea is so clearly defined in the inventor's mind that only ordinary skill would be necessary to reduce the invention to practice, without extensive research or experimentation. Sewall v. Walters, 21 F.3d 411, 415, 30 USPQ2d 1356, 1359 (Fed. Cir. 1994). Since the applications are copending the burden is on Weissmann to prove his case by a preponderance of the evidence. Davis v. Reddy, 620 F.2d 885, 888, 205 USPQ 1065, 1068 (CCPA 1980).

For derivation, Weissmann (WB 46-47) alleges that (1) Goeddel et al. had a copy of the Weissmann Nagata Nature preprint (WX Haley, X5048-5080) in their files (2) Goeddel learned of the DNA and amino acid sequence of Weissmann's mature interferon by telephone from Roche's Weissbach and (3) Goeddel et al. had a copy of the DNA and amino acid sequence of Weissmann's leukocyte interferon as evidenced by their appearance in the Yelverton notebook.

While Weissmann presented no evidence to establish that Goeddel et al. was in possession of the Nagata preprint as of April 15, 1980, that is of no moment, since the Nagata preprint itself was published March 27, 1980 and therefore available as prior art. This publication[FN28] describes Weissmann's microbial production of a polypeptide having interferon activity but does not disclose a DNA or amino acid sequence for the polypeptide. In any event, the polypeptide described in Nagata is not a compound within the scope of the count.

We agree with Weissmann that at least by April 15, 1980, Goeddel et al. were in possession of the DNA sequence and the corresponding deduced amino acid sequence which codes for Weissmann's mature interferon as evidenced by the presence of a pasted copy of the DNA and deduced amino acid sequence of mature human leukocyte interferon identified as "Weissmann huleukIF sequence" in the notebook of Yelverton, a technician in the laboratory of David Goeddel. See Yelverton testimony (GR 940-942) and undated notebook page 45980 (GX Yelverton Cross Exhibit 34). Note that page 45983 is dated 4-15-80. Thus, the issue is whether a description of a compound by itself, that is, the amino acid sequence of mature human leukocyte interferon, is sufficient to establish conception.

***16** Weissmann has provided no evidence to show that a method of making a compound within the scope of the art was well known. Rather, he relies upon the combination of (1) the method of making a polypeptide having interferon activity, a compound outside the scope of the count found in Nagata publication, (2) the possession by Goeddel et al. of Weissmann's DNA sequence and corresponding deduced amino acid sequence, (3) the Goeddel et al. Nature article or EPO 1929 publication to establish that one skilled in the art would have been enabled to microbially produce a compound of the count.

Conception of a compound requires both the idea of the invention's structure and possession of an operative

method of making it. Oka v. Youssefyeh, 849 F.2d 581, 583, 7 USPQ2d 1169, 1171 (Fed. Cir. 1988). When, as is often the case, a method of making a compound with conventional techniques is a matter of routine knowledge among those skilled in the art, a compound has been deemed to have been conceived when it was described, and the question of whether the conceiver was in possession of a method of making it is simply not raised. Id. In this instance, we do not find that possession of the amino acid sequence is sufficient to establish conception of the count for the reasons set forth above in regard to the enablement issue. Simply put, this record does not establish that one skilled in this art would have been able to make a compound of the count as of April 3, 1980 without undue experimentation. Thus, whether in the context of the enablement of the April '80 EPO application or the purported derivation of the invention from Weissmann by Goeddel et al., knowledge of the nucleotide/amino acid sequences by themselves or in the context of the Goeddel Nature article or EPO 1929 would not have enabled one skilled in the art to make mature human leukocyte interferon of the count without undue experimentation.

Having found no conception, we find no derivation.

Issue (5)

The Weissmann motion to amend his preliminary statement.
The motion is dismissed as moot.

In his original preliminary statement (Paper No. 29), Weissmann stated, in paragraph 14, that the earliest date that he had communicated his invention to opponents was at an April 15, 1980 seminar in Paris. In paragraph 14 as amended, in the motion to amend (Paper No. 171), Weissmann now alleges four dates earlier than April 15, 1980 where he allegedly communicated his invention to his opponents.

Even assuming arguendo that Weissmann (1) satisfied the requirements of 37 CFR 1.628(a) to correct the preliminary statement and (2) relied upon and proved the earlier alleged dates for communication, he would be in no better position with respect to the alleged earlier dates since he has not established conception.

Issue (6)

The APJ's denial of the Weissmann motion to add counts 3-7 to this proceeding. [IIC1]
***17** Weissmann brought this motion (Paper No. 26), alleging that the restriction requirements made by the primary examiners in the involved Goeddel et al. and Weissmann applications during ex parte prosecution establish that counts 3-7 are separately patentable and thus they should be added to this proceeding. The APJ denied the motion stating that Weissmann had not sustained his burden of proof to establish separate patentability of the counts.

In their brief, Weissmann reiterate the same position set forth in the motion paper. We have reviewed the APJ's decision, however we find no abuse of discretion. Restriction practice is discretionary on the part of the PTO. Pointing to the prosecution history to show what the primary examiner did during ex parte prosecution does not satisfy the burden of the movant to show separate patentability within the meaning of 37 CFR §1.601(n). As noted by the rules, the standard of separate patentability is that of novelty and obviousness not that of restriction. Weissmann has not addressed this issue. The decision of the APJ is affirmed.

Issue (7)

The APJ's denial of the Goeddel et al. motion for judgment on the ground that Weissmann claims 37-39 and 41 and 42 are unpatentable over the Goeddel Nature Paper and Streuli Science Paper

The motion is dismissed as moot in view of our holding in Issues (2), (3) and (4), supra.

We make one additional observation and comment. In the brief, Goeddel et al. now allege that Weissmann claims 37-39, 41 and 42 are unpatentable over the Goeddel Nature article alone, in view of a public lecture by Heynecker at a September 8-9, 1980 NIH Interferon workshop [the Heynecker speech] (WR 1227; WX 67 at B35063) in combination with Streuli Science Paper (WX Weissbach 37). Goeddel et al. are now alleging for the first time in their brief that these claims are unpatentable over the Heynecker speech. The reliance on the Heynecker speech is new, raised for the first time in the Goeddel et al. brief. Hence, reliance on the Heynecker speech is improper, not entitled to any consideration by the Board and is therefore dismissed.

Issues (8) and (9)

The APJ's denial of the Goeddel et al. motion to designate Weissmann et al claims 37-39 and 41 and 42 and Goeddel claims 4 and 8 as not corresponding to count 1. [IA1 and IA2] and the Goeddel belated motions for judgment on the grounds of lack of best mode.

Consideration of these issues is deemed moot in view of the disposition of the issues of priority, enablement and derivation.

Issues (10) and (11) (a)

Weissmann's motion to file a belated supplemental §1.682 notice and to supplement the Weissmann record And the Goeddel et al. motion to strike or deny consideration to portions of Weissmann motion or to return the motion as an unauthorized paper.

The Weissmann motion is granted and the Goeddel et al. motion is denied.

***18** On February 22, 1991, Weissmann moved to file a supplemental notice listing a paper dated December 20, 1990 and filed by Genentech, co-assignee of the involved Goeddel et al. application, in the European Patent Office during an opposition proceeding relating to EPO 1929 and to include the paper in his record.

Goeddel et al. object to the filing of the supplemental notice and to the entry of the paper for two reasons (1) the notice is untimely since it was filed after the close of the Weissmann testimony period and (2) a certified copy of the official record was not filed with the motion.

As to (2), Weissmann has now filed the certified copy (Paper No. 252) and the Goeddel et al. objection is moot. As to (1), Goeddel et al. point out that the motion was filed the day before Goeddel et al. was to file its main brief. Goeddel et al. urge that it is manifestly unfair to be faced with this new document at this time since they were denied the right to present rebuttal evidence and deprived of an opportunity to consider the full scope of the evidence when filing their brief.

We agree with Weissmann that the document was submitted as soon as possible after it was received. The allegations of Goeddel et al. as to their purported denial to present rebuttal or time to consider the evidence when filing the brief are not persuasive arguments since Goeddel et al. could have requested an extension of time to consider the evidence before filing their brief or requested an opportunity to present rebuttal evidence by requesting that their testimony period be reopened for that purpose. No such request was made.

Therefore, the evidence will be entered for the purpose of rendering a complete decision.

The Goeddel et al. motion to strike or deny consideration to portions of Weissmann motion or to return the motion as an unauthorized paper is denied. The Weissmann motion is not an unauthorized paper.

Issues (11) (b), (c) and (d)

(11) (c) and (d) Goeddel's Motion to Suppress

The Goeddel et al. motion moved to suppress (1) the first declaration of Walter Gilbert executed March 18, 1988, (2) Weissmann Exhibit Bullock 1, a memorandum dated May 19, 1980 authored by Drs. Leibowitz and Ryan as inadmissible hearsay, and (3) a memorandum by George Gould identified, inter alia, as Weissmann Exhibit (Haley) 33, Weissmann Exhibit (Sharp) 14 and Goeddel (Weissbach) Deposition Exhibit 33 as inadmissible non-authenticated hearsay.

As to (1), the motion is dismissed as moot since Weissmann acknowledges that the inclusion of the first Gilbert declaration was inadvertent and that Weissmann would not and have not relied on the declaration. Nor have we.

As to (2), the motion is granted for essentially the reasons set forth in the Goeddel et al. motion and associated reply. Weissmann does not challenge the Goeddel et al. charge of hearsay. Rather he urges that the memo is admissible under FRE 803(6) as a record of regularly conducted activity and that Bullock became the custodian of the memo when Liebowitz left the employ of Schering. However, the record clearly indicates that the memo before us is not the memo from the Leibowitz files to which Bullock was custodian but rather a memo that Bullock supposedly received from Daniels, annotated and placed in his own files. To the extent that Weissmann relies upon the memo for the opinions of Leibowitz and Ryan, who did not testify, the exhibit is hearsay. Contrary to the Weissmann allegations, it does not qualify as a record of regularly conducted activity (FRE 803(6)) for the reasons set forth in the Goeddel et al. reply (Paper No. 249).

***19** As to (3), the motion is denied. The exhibit is a memo dated July, 1979 addressed to Dr. J.J. Burns, by George Gould, then Assistant Patent Counsel for Roche, co-assignee of the involved Goeddel et al. application in which Gould iterates statements made to him in telephone conversations by Bob Swanson, the president of co-assignee Genentech. Goeddel et al. themselves introduced this memo into the record during their testimony. (GR 189 and 195). Goeddel et al. now object to the admission of the exhibit on the ground that by choice Gould was not cross-examined with respect to the memo and that the memo is inadmissible, non-authenticated hearsay. Weissmann allege that the Gould memo is admissible as admissions of a party opponent. FRE801(d)(2(A).

It is inappropriate for Goeddel et al., simply because Weissmann relies upon it, to move to suppress evidence which they themselves introduced into the record. Cf. In re Hedges, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986) [An applicant supplying references cannot object to the PTO's citation of other portions of the same reference].

(11) (b). Weissmann motion to suppress

Weissmann moved to suppress Goeddel Weissbach Deposition Exhibit 30, a document entitled "FDA Seminar on the State of the Art in Recombinant DNA Research", dated June 4, 1980 as hearsay.

Since we have not relied on this document in making our determinations, we find it unnecessary to address the Weissmann motion to suppress.

Decision

In view of the foregoing, priority is awarded to Goeddel et al. On this record, Judgment is awarded against Weissmann, and Weissmann is not entitled to a patent containing claims 37-39, 41, 42, 77-79, 85 and 87 corresponding to the count. Judgment is awarded to David V. Goeddel and Sidney Pestka, and they are entitled to a patent containing claims 1-4, 8 and 52-69 corresponding to the count.

BOARD OF PATENT APPEALS AND INTERFERENCES

RONALD H. SMITH

Administrative Patent Judge

MARY F. DOWNEY

Administrative Patent Judge

WILLIAM F. SMITH

Administrative Patent Judge

FN1. Application 06/256,204, filed April 21, 1981.
Accorded the benefit of Application 06/164,986, filed July 1, 1980, application 06/205,578, filed November 10, 1980, application 06/184,909, filed September 8, 1980.
Assignor to Genentech, Inc. and Hoffmann-LaRoche Inc.

FN2. Application 06/471,301, filed March 2, 1983.
Accorded the benefit of Application 06/223,108, filed January 7, 1981, European Patent Application 80301100.6, filed April 3, 1980, United Kingdom Patent Application 8031737, filed October 2, 1980.
Assignor to Biogen N.V.

FN3. APJ William F. Smith has been substituted for APJ Goolkasian who has retired. Cf. In re Bose Corp., 772 F.2d 866, 868-869, 227 USPQ 1, 2-4 (Fed. Cir. 1985).

FN4. Hoffmann-LaRoche Inc. (Roche) granted Schering Corporation (Schering) certain non-exclusive rights under the Goeddel et al. applications and also granted such rights to Biogen N.Y., as remainderman, under certain circumstances (See Paper No. 12).

FN5. Biogen N.V. granted Schering and its affiliates an exclusive field of use license and Schering granted a non-exclusive field of use sublicense and immunity from suit under this patent application to Roche and an option for a non-exclusive field of use sublicense and immunity from suit under the patent application to Genentech Inc. (See Paper No. 10).

FN6. The Commissioner of Patents and Trademarks authorized Examiners-in-Chief to use the title Administrative Patent Judge (APJ) for business-related activities. See Commissioner's Notice of Oct. 15, 1993, New Title for Examiners-in-Chief, 1156 Off. Gaz. Patent & Trademark Office 32 (Nov. 9, 1993).

FN7. The interference is being concurrently redeclared to reflect the granting of these motions.

FN8. After the decision on preliminary motions had been rendered, Goeddel et al. filed a belated motion (37 CFR §1.633(g)) to deny benefit accorded Weissmann of his earlier filed foreign applications for failure to disclose the best mode (Paper No. 118). The motion was dismissed. See Paper No. 126.

FN9. The Weissmann and Goeddel et al. records will be referred to as WR and GR. The parties briefs and exhibits will be referred to in a like manner, WB, GB, WX and GX, followed by the appropriate number.

FN10. 37 CFR 1.655(a), has now been amended, 60 Fed. Reg. 14488-536 (March 17, 1995) and reads in part:

> All interlocutory orders shall be presumed to have been correct, and the burden of showing an abuse of discretion shall be on the party attacking the order.

FN11. In view of the fact that Weissmann has conceded to Goeddel et al. the date of May 16, 1980 for priority purposes, we do not find it necessary to address whether Weissmann is entitled to the benefit of the October 2, 1980 filing date of the UK application.

FN12. Goeddel et al. in their motion originally argued that the April '80 EPO application, despite the disclosure of the amino acid sequence of a single polypeptide of 166 amino acids corresponding to a mature human leukocyte interferon within count 1, namely IFN-<<alpha>> 1 (see original claims 25, 37, 43, 64, 70 and Fig. 8-10), did not satisfy the written description requirement of 35 USC 112, first paragraph, because the application failed to describe a method of making the compound. That argument has not been raised in their brief. Matters not raised in the brief are ordinarily considered abandoned. Photis v. Lunkenheimer, 225 USPQ 948, 950 (Bd. Pat. Int. 1984).

FN13. Goeddel et al., Direct Expression in *Escherichia coli* of a DNA Sequence Coding for Human Growth Hormone, Nature, Vol. 281, pp. 544-548 (October 18, 1979).

FN14. EPO No. 1929, a patent publication to Itakura et al., assigned to Genentech, Inc., published May 16, 1979. This publication is the equivalent of UK 2,007,676A, published May 23, 1979 and relied upon by Weissmann in his opposition paper.

FN15. A product-by-process claim normally is an after-the-fact definition, used after one has obtained a material by a particular process. Fiers v. Sugano, 984 F.2d 1164, 25 USPQ2d 1601 (Fed. Cir. 1993).

FN16. We have not been asked, nor do we find it necessary to address whether the claims of the parties embrace a naturally occurring product. This issue can and should be addressed ex parte after the termination of the interference.

FN17. The April '80 EPO application describes the preparation of the polypeptide product by preparing poly(A) RNA containing human leukocyte interferon mRNA from virus induced human leukocytes, preparing single-stranded complementary cDNA therefrom, converting the single stranded cDNA to double-stranded form, elongating the double-stranded cDNA with dCMP tails, annealing the tailed cDNA with a tailed vector, pBR322 cleaved at PstI site and tailed with dGMP tails, and transforming E. coli with the annealed product to make a library. Thereafter, the library was screened for a clone hybridizing to human leukocyte interferon mRNA by means of a hybridization translation assay. A clone designated Hif-2h was isolated and characterized. See Pages 14-51 of the application; WR 1097-1108, WR 263-266 and WR 820-822.

FN18. Transcript of Tape Recorded Press Conference in Boston, Mass. at the Park Plaza Hotel, January 16,

1980.

FN19. Weissmann, "The Cloning of Interferon and Other Mistakes", Interferon, Vol. 3, pp. 101-134 (1981).

FN20. Weissmann when questioned as to whether the EPO application contained a method of making a compound of the count stated:

> As a matter of principle, I had not introduced, to the best of my knowledge, protocols for things we had not done. And since we had at that time not really done anything which was specifically aimed at generating mature or met-mature interferon, I would not have put in such a protocol.

FN21. Somatostatin and insulin do not contain methionine residues except for the inserted start codon.

FN22. See Goeddel et al., "Synthesis of Human Fibroblast Interferon by E. coli," Nucleic Acids Research, Vol. 8, No. 18, pp. 4057-74 (September, 1980). Goeddel First Declaration Ex. C.

FN23. It would appear that one example in Table 1 would appear to support the Goeddel et al. position of unpredictability in the art at this time. In that Table, there is one extract which does not result in any HGH activity in the radioimmunoassay. No explanation is provided for the lack of activity. However, Weissmann has not addressed any specific example with any reasonable degree of specificity nor has he provided testimony which specifically analyzed the expression method therein or explained how that method could be directly applied to interferon. Cf. Martin v. Johnson, supra.

FN24. The Bullock memo, dated May 19, 1980, containing the statements of Leibowitz and Ryan was subject to a motion to suppress which has been granted, see infra. The evidence is not properly before us, and even if it were, it would not be relevant since it is not reflective of what one of ordinary skill in the art knew as of April 3, 1980.

FN25. Taniguchi et al., "Expression of the Human Fibroblast Interferon Gene in Escherichia coli," Proc. Natl. Acad. Sci, Vol. 77, No. 9, pages 5230-33 (September 1980) (Goeddel Second Declaration, Ex. D).

> This article reports that upon pulse-chasing human fibroblast pre-interferon containing 187 amino acids is completely degraded at 50 minutes and the mature fibroblast containing 166 amino acids is 50% degraded after 50 minutes. Both parties rely upon this article alleging that it supports their respective positions. Goeddel et al. argues that this article shows that stability of one form of protein is not predictive of stability of another form of that protein (GR 2077-78, GB 86 n.58). Goldberg opines that this article shows that the mature protein is more stable than its corresponding preprotein and thus one would expect the mature human leukocyte interferon to be more stable than the preprotein (WR 430-431).

FN26. The fact that stability and degradation were concerns as of April 3, 1980 is also supported by the April '80 EPO application itself, page 23, which indicates that the selection of vectors and hosts is determined by "susceptibility of the desired protein to proteolytic degradation by host cell enzymes". Stability also appeared to remain a concern at the time testimony was taken. Dr. Weissmann, himself testified when asked what effect the differing stabilities of preinterferon fibroblast and mature fibroblast interferon have upon the predictability of the stability of mature alpha interferon and met-mature alpha interferon in E. coli, that he could not conclude anything from the Taniguchi publication because "certainly at that time, and even today very little is known about what makes a protein more or less stable in E. coli, and the differences between fibroblast interferon and leukocyte interferon were too substantial to allow any reasonable deductions to be made from one to the other." (WR 1137). Dr. Weissmann's testimony would appear to be in conflict with Goldberg's view that Taniguchi et

al. supports his view.

FN27. Weissmann deviated from the procedure disclosed in the Goeddel Nature article in that he synthetically attached the first codon, TGT, via the Hin dIII (Wu) linker, to the mature sequence which had been partially digested with a restriction endonuclease (Sau3A), to rebuild the mature sequence. He did not ligate ATG to the mature sequence as in the Goeddel Nature article, but rather used a linker oligonucleotide, provided by Collaborative Linker, to provide an ATG start codon to the lac promoter. The two constructions were ligated to provide a lac promoter flanked on its downstream side by an EcoRI site, a small piece of plasmid and a HindIII site flanked by the mature coding sequence, this construct was then cleaved with EcoRI and HindIII and digested to remove the overhanging ends, fused to position the promoter-ATG to the first codon of the mature sequence. (WR 1204-1214)

FN28. Nagata et al., "Synthesis in E. coli of a Polypeptide with Human Leukocyte Interferon Activity," Nature, Vol. 284, pp 316-320 (March 27, 1980). WX Gilbert 6.

1995 WL 17831418 (Bd.Pat.App. & Interf.)
END OF DOCUMENT

PATENT OFFICE
JAPANESE GOVERNMENT

This is to certify that the annexed is a true copy of the following application as filed with this Office.

DATE OF APPLICATION: March 19, 1980

APPLICATION NUMBER: 33931/80

APPLICANT(S): Juridical Foundation, Japanese Foundation for Cancer Research

Dated this 31st day of October, 1980

Haruki Shimada
Director-General
Patent Office

Certified No. SHO 55-30589

Application for Patent

March 19, 1980

To: Mr. Yoshio Kawahara,
Director General of Patent Office

1. Title of the Invention

Novel recombinant plasmids having the human fibroblast interferon messenger RNA gene

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5. List of the Annexed Documents

1)	Specification	one copy
2)	Drawing	one copy
3)	Power of Attorney	one copy
4)	Duplicate of the Application	one copy

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Specification

1. Title of the Invention

Novel recombinant plasmids having the human fibroblast interferon messenger RNA gene

2. Scope of Claim for Patent

(1) Novel recombinant plasmids that are made by inserting a DNA synthesized with human fibroblast interferon messenger RNA as a template into a vector plasmid DNA, having a gene which encompasses at least the entire coding region of the human fibroblast interferon messenger RNA.

(2) The novel recombinant plasmid in claim 1, wherein the recombinant plasmid is an Escherichia coli plasmid DNA.

3. Detailed Description of the Invention

This invention relates to novel recombinant plasmids having the human fibroblast interferon messenger RNA gene.

Interferon is a glycoprotein (molecular weight approx. 20,000) with antiviral activity, discovered by Isaacs and Lindenmann in 1957. Subsequent studies have revealed its antitumor activity besides its antiviral activity and hence a wide clinical application of this substance has gradually started. For instance, it is reported that this substance is effectively administered to various viral diseases, osteosarcoma and mammary carcinoma.

However, because of its high species-specificity, only the interferon derived from human cells can be used for human application. At present, the interferon which is being used for administration has a relative activity of about 10^6 (International units) per 1 mg, which corresponds to the purity of about 0.1 - 0.01%.

Further, the wide use of the interferon is impossible because of the difficulty of its mass-production.

At present even for the interferon requirement for clinical tests (10^{13} units per year), the supply is only about 1%. For these reasons, development of technology to produce human interferon with a high purity easily and also in large quantities is desired.

The present inventors thought that it was the novel technique for producing interferon with ease and in a large quantity to insert a human interferon gene into a plasmid DNA (for instance plasmid DNA derived from Escherichia coli) with the recombinant DNA (deoxyribonucleic acid) technology. The inventors have completed this invention based on the thought.

That is, this invention relates to a novel recombinant plasmid, having a gene which encompasses at least the entire coding region of the human fibroblast interferon messenger RNA, in which a DNA synthesized using the human fibroblast interferon messenger RNA (ribonucleic acid) as a template is inserted into a vector plasmid DNA. The aim of this invention is to provide novel recombinant plasmids which grow and amplify in bacteria such as Escherichia coli and, as a result, can be used to produce human fibroblast interferon in bacteria such as Escherichia coli.

"The entire coding region" means the part specifying the whole amino acid sequence of the protein of the human fibroblast inteferon in the human fibroblast interferon messenger RNA sequence.

The novel recombinant plasmid (or recombinant plasmid DNA) having a gene which encompasses the entire coding region of the human fibroblast interferon messenger RNA has been obtained for the first time by the present inventors. The novel recombinant plasmid is a very useful substance which may be used for amplification in bacteria such as Escherichia coli and production of human fibroblast interferon in large quantities and at low cost.

The novel recombinant plasmid of this invention can be obtained by the following procedure. First, cytoplasmic RNA is extracted from either human fibroblast,

MG63 cells or others induced by poly(I)(C) which is a double-stranded RNA composed of polyinosinic acid and polycytidylic acid and is sold by the U.S. CALBIOCHEM Co. etc., or NAMALVA cells or others induced by Sendai virus. From this RNA, the human fibroblast interferon messenger RNA (hereinafter messenger RNA is referred to as mRNA) containing poly A (polyadenylic acid) is isolated. A double-stranded DNA is synthesized by reverse transcriptase, etc. with the mRNA portion having high interferon mRNA activity as a template. A recombinant is obtained by inserting the synthesized DNA into a vector DNA such as Escherichia coli plasmid DNA by the technique of recombinant DNA. The recombinant is labelled with a radio isotope to use as a probe. A recombinant plasmid having an inserted portion which codes the entire protein of the human fibroblast interferon is selected from said synthesized recombinant DNA.

The process of producing the present recombinant plasmid is explained in detail below.

First, human fibroblasts may be obtained from fetus-derived foreskin, etc.

A small amount of interferon is added to the culture fluid of human fibroblasts to prime production of interferon by human fibroblasts, to which poly(I)(C) is added to induce the production of interferon. Cycloheximide is added simultaneously to increase the production of interferon (superinduction) and the level of interferon mRNA. At an appropriate time (e.g. 4 hours) after human fibroblasts are superinduced in this way, cells are collected and destroyed and nuclei are removed. Cytoplasmic total RNA is extracted with phenol, etc. RNA can also be extracted by destroying the whole cells, extracting both DNA and RNA with phenol, etc. and degrading and removing DNA with DNAase.

Further, RNA can also be extracted from MG63 cells which can be obtained from patients of osteosarcoma, etc. instead of human fibroblasts, by inducing as described above.

Furthermore, RNA can be induced in MG63 cells which can be obtained from patients of osteosarcoma or NAMALVA cells which can be obtained from lymphoma patients by incubation with Sendai virus (which can be obtained from medical schools), etc. and extracted therefrom as described above.

The thus extracted RNA is dissolved in a salt solution with a high concentration (e.g. solutions of NaCl and KCl) and put on a column of oligo (dT) cellulose sold by P-L Biochemicals Co., USA to adsorb mRNA having poly(A) on the column. Elution is carried out with water, a salt solution with a low concentration such as 10 mM Tris-HCl buffer, or the like to isolate mRNA having poly(A).

The isolated mRNA is fractionated according to the difference mainly in molecular weight by sucrose density gradient centrifugation. Interferon mRNA activity in each fraction is checked by determining interferon activity (antiviral activity) of the protein which is synthesized in oocytes of African claw toad (Xenopus leavis) by micro-injecting a part of the fraction.

Then, a DNA complementary to the mRNA is synthesized in vitro by a reverse transcriptase, which is obtained from avian myeloblastosis virus, using an mRNA having the highest specific activity fraction as the template.

The synthesis is carried out as follows.

An mRNA is reacted at an appropriate temperature (e.g. 37°C) for an appropriate period (e.g. 60 min.) with oligo(dT) sold by P-L Biochemicals Co., USA, $MgCl_2$ (e.g. 5 mM), NaCl (e.g. 30 mM), mercaptoethanol (e.g. 5 mM) and Tris-HCl buffer (e.g. pH 8.0, 40 mM) using a reverse transcriptase together with deoxyadenosine triphosphate (dATP), deoxythymidine triphosphate (dTTP), deoxyguanosine triphosphate (dGTP) and deoxycytidine triphosphate (dCTP) (e.g. 0.5 mM each) as substrates.

The thus obtained reaction product containing mainly DNA is subjected to deproteinization with phenol, etc. and the template RNA is removed by alkali treatment. A double-stranded DNA is synthesized by a reverse transcriptase

in a similar way as the synthesis of the DNA complementary to mRNA described above except that mRNA is replaced by DNA and oligo(dT) is excluded.

Incidentally, by using Escherichia coli DNA polymerase I which can be obtained from Escherichia coli MRE 600, etc. instead of reverse transcriptase, the same double-stranded DNA can be synthesized.

After the double-stranded DNA which is synthesized by the above described procedure is treated with Nuclease S_1 which can be obtained from Aspergillus oryzae in the presence of $ZnCl_2$ (e.g. 1 mM), sodium acetate buffer (e.g. 0.1 M, pH 4.5), NaCl (e.g. 0.2 M), etc., deoxyadenine chains are formed at both 3' ends of the synthesized DNA by incubating with a terminal transferase (e.g. sold by Bethesda Research Laboratories, USA) purified from calf thymus in the presence of potassium cacodylate buffer (e.g. pH 7.6, 0.14 M), Tris (base) (e.g. 0.03 M), dithiothreitol (e.g. 0.1 mM), $CoCl_2$ (e.g. 1 mM) and dATP (e.g. 1mM) at an appropriate temperature (e.g. 37°C) for an appropriate period (e.g. 20 min.).

On the other hand, a plasmid DNA which is used as a vector DNA, e.g. Escherichia coli plasmid pBR322 DNA [Gene vol.2, p.95-113 (1977)], is cut at one site by treating with a restriction endonuclease EcoRI, which can be obtained from Escherichia coli RY13 etc., in the presence of Tris-HCl buffer (e.g. pH 7.5, 10 mM), $MgCl_2$ (e.g. 6 mM), NaCl (e.g. 0.1 M), mercaptoethanol (e.g. 6 mM), etc. and then treated with phage λ-derived exonuclease, which can be obtained from Escherichia coli W3102 (λ cI851 x 13), etc., in the presence of Na-glycine buffer (e.g. pH 9.5, 0.1 M), $MgCl_2$ (e.g. 5 mM), etc. Thereafter deoxythymidine chains are formed at both 3' ends in the same way as for the above-described synthesized double-stranded DNA by using dTTP instead of dATP.

Synthetic double-stranded DNA and plasmid DNA which are chain-elongated at both 3' ends as described above are incubated at an appropriate temperature for an appropriate period with Tris-HCl buffer (e.g. pH 7.5, 50 mM),

NaCl (e.g. 0.1 M), EDTA (e.g. 5 mM), etc. and hybridized with hydrogen-bonds of adenine and thymine. Then, a transformable Escherichia coli strain, e.g. Escherichia coli χ 1776 [Molecular Cloning of Recombinant DNA, Scott, W. A. & Werner, R. edited, Academic Press p.99-114 (1977)] is transformed with the hybridized DNA by the method of Enea et al. (J. Mol. Biol. vol.96, p.495-509, 1975) or the like.

In the novel recombinant plasmid DNA thus obtained there exists a vector DNA gene, e.g. β-lactamase (enzyme that destroys ampicillin) gene, of Escherichia coli plasmid pBR322. Therefore, the transformed Escherichia coli shows resistance to ampicillin. The following technique is used to pick up a strain with a novel recombinant having a gene which shows complementarity to the human interferon messenger RNA among these ampicillin resistant strains.

First, [^{32}P] labelled DNA is synthesized with the RNA having interferon mRNA activity described above as a template and the DNA is hybridized with mRNA extracted, without induction by poly(I)(C) (therefore, this mRNA does not contain interferon mRNA), from the human fibroblast by incubating at a high temperature (e.g. 65°C) in a reaction mixture containing NaCl (e.g. 0.5 M) etc. Then, the hybridized DNA (Probe A) and non-hybridized DNA (Probe B) are separated by hydroxyapatite column chromatography. Next, filter-fixed DNAs of transformants are hybridized separately with Probe B or Probe A according to the tehcnique of Grunstein-Hogness [Proc. Nat. Acad. Sci. USA, vol.72, p.3961-3965 (1975)] and strains having a DNA hybridizable with Probe B but not or hardly with Probe A are discerned by autoradiography.

Then, plasmid DNA is isolated from the thus discriminated strain and hybridized with mRNA having interferon mRNA activity by incubating at a high temperature (e.g. 53°C) in the presence of 80% (w/v) formamide, 0.4 M NaCl, etc. Since the mRNA hybridized with the plasmid DNA from the above-described strain does not pass through nitrocellulose filter and is trapped, this mRNA is eluted from the filter at a high temperature (e.g. 60°C) with a solution such as

90 % (v/v) formamide and injected into oocytes of African claw toad and interferon activity is determined as described above.

When interferon activity is determined to be positive with this procedure, the DNA used for hybridization is concluded to be a DNA having a base sequence complementary to interferon mRNA and by this method, a recombinant plasmid DNA having a gene complementary to the human fibroblast interferon mRNA can be discriminated.

The recombinant plasmid DNA obtained above or segments cut with a restriction endonuclease are labelled with a radio isotope such as ^{32}P by Nick-translation method [Rigby, et al., J. Mol. Biol. Vol.113, p.237-251 (1977)], etc. and used as a probe to obtain Escherichia coli strains containing a recombinant plasmid having interferon mRNA sequence from the above ampicillin-resistant strains in the same way as above. Many strains thus obtained are cultured and the plasmid DNA is isolated therefrom. The plasmid DNA is cut with a restriction endonuclease to cbtain the inserted mRNA. The length of the inserted mRNA is investigated to gain a plasmid having an inserted mRNA coding the entire region of interferon protein. Primary structure of the recombinant plasmid is determined according to Maxam-Gilbert method [Proc. Nat. Acad. Sci. U.S.A. vol.74, p.560-564, 1977]. It has been proved that the recombinant plasmid contains the entire gene which codes the protein of the human fibroblast interferon mRNA.

The present novel recombinant plasmids having a gene which encompasses at least the entire coding region of the human fibroblast interferon mRNA are very useful because they enable mass production of interferon in Escherichia coli or in eukaryotic cells which can be grown in a large scale.

The invention will be explained more in detail in the following example. However, this invention will not be restricted thereto.

Example:

After priming of human fibroblasts by overnight incubation with MEM culture medium containing interferon (25 U/ml), they were superinduced by adding 10 µg/ml of poly(I)(C) and 5 µg/ml of cycloheximide to the medium.

After 4 hours, 10^9 superinduced human fibroblasts were destroyed by Teflon homogenizer in the presence of 0.3 % NP-40 and 50 µg/ml heparin in RSB buffer (10 mM Tris-HCl, pH 7.5; 10 mM NaCl; 1.5 mM $MgCl_2$). Nuclei were removed by centrifugation and 9.6 mg of cytoplasmic RNA was obtained by extracting 3 times with phenol.

The cytoplasmic RNA was precipitated with ethanol, dissolved in 10 ml of 1 mM EDTA solution and incubated at 65°C for 2 minutes. 2.5 ml of a salt solution with a high concentration (0.5 M Tris-HCl, pH 7.5 ; 1 M NaCl ; 50 mM EDTA) was added to the above solution and the mixture was put on an oligo(dT) cellulose column to adsorb mRNA containing poly(A). Elution was carried out with a salt solution with a low concentration (10 mM Tris-HCl, pH 7.5) and water to isolate 250 µg of mRNA containing poly(A).

The mRNA was precipitated with ethanol and dissolved in 0.5 ml of 1 mM EDTA solution. The solution was incubated at 65°C for 2 minutes, subjected to centrifugation through a 5 - 25% sucrose-density gradient (rotated at 35,000 rpm using the SW40 rotor of Beckmann Co., U.S.A.) at 4°C for 16 hrs, and fractionated into 20 fractions.

The interferon mRNA activity of each of these fractions was determined as mentioned above. The result is shown in Table 1.

Table 1

Fraction No.	Interferon Activity
9	< 50 units/ml
10	44
11	550
12	52

mRNA in Fraction No. 11 was approximately 5 µg. The mRNA and a reverse transcriptase were incubated at 37°C for an hour in 20 µl of a reaction mixture [5 µg mRNA; 1 µg oligo(dT); 8 units reverse transcriptase; 5 mM $MgCl_2$; 30 mM NaCl; 5 mM mercaptoethanol; 40 mM Tris-HCl, pH 8.0] and deproteinized with phenol. After RNA was removed by the treatment with 0.3 N NaOH at 37°C for 15 hours, the synthesized single-stranded DNA was incubated at 37°C in 20 µl of a reaction mixture [the same mixture as described above except that mRNA and oligo(dT) were excluded] for an hour to synthesize 1.5 µg of a double-stranded DNA.

The double-stranded DNA was treated with Nuclease S_1 in 50 µl of a reaction mixture (1.5 µg double-stranded DNA; 1 mM $ZnCl_2$; 0.1 M sodium acetate, pH 4.5; 0.2 M NaCl; 0.05 unit S_1) at 37°C for 30 minutes and the enzyme was removed with phenol. The DNA was precipitated with ethanol and then treated with a terminal transferase in 20 µl of a reaction mixture [1.5 µg DNA; 0.14 M potassium cacodylate, pH 7.6; 0.03 M Tris (base); 0.1 mM dithiothreitol; 1 mM $CoCl_2$; 1 mM dATP; 1 unit terminal transferase] at 37°C for 20 minutes. Thus about 100 deoxyadenosine chains were formed at both 3' ends of the double-straded DNA.

On the other hand, 10 µg of Escherichia coli plasmid pBR322 DNA was treated at 37°C for 2 hours with a restriction endonuclease EcoRI in 100 µl of a reaction mixture (10 mM Tris-HCl, pH 7.5; 6 mM $MgCl_2$; 0.1 M NaCl; 6 mM mercaptoethanol; 10 units EcoRI) leading to the cleavage at the only one cutting site in pBR322 DNA. The cut plasmid DNA was treated with an exonuclease derived from phage λ in 200 µl of a reaction mixture (10 µg DNA; 0.1 M Na-glycine, pH 9.5; 5 mM $MgCl_2$; 50 µg/ml albumin; 17.5 units λ exonuclease) at 0°C for 90 minutes and the enzyme was removed with phenol. The DNA was treated with a terminal transferase in 50 µl of a reaction mixture (10 µg DNA; 0.14 M potassium cacodylate, pH 7.6; 0.03 M Tris (base); 0.1 mM dithiothreitol; 1 mM $CoCl_2$; 1 mM dTTP; 2 units terminal transferase) at 37°C for 20 minutes. This led to the elongation of about 100 deoxythymidine

chains on both 3' ends of plasmid pBR322 DNA described above.

0.02 µg of the synthesized double-stranded DNA thus obtained, and 0.1 µg of the plasmid pBR322 DNA were incubated for hybridization in a solution containing 0.1 M NaCl, 50 mM Tris-HCl (pH 7.5) and 5 mM EDTA at 65°C for 2 minutes, at 45°C for one hour, at 37°C for one hour and at room temperature for one hour. Then, Escherichia coli χ 1776 was transformed with the hybridized recombinant following the method of Enea et al.

About 4,000 ampicillin-resistant strains were isolated in this way. 3,600 resistant strains were chosen, and each DNA was fixed on two nitrocellulose filters (Grunstein-Hogness Method).

On the other hand, [^{32}P] labelled single-stranded DNA was synthesized (about 0.44 µg, specific radioactivity approx. 6×10^8 c.p.m./µg) by a reverse transcriptase in the same way as that for single-stranded DNA mentioned above (dCTP was labelled with ^{32}P) using the interferon mRNA fraction (about 10 µg) which had been extracted and partially purified as described above, as a template. The DNA was hybridized in 50 µl of a reaction mixture (25 µg mRNA; 0.45 µg single-stranded DNA labelled with ^{32}P; 0.5 M NaCl; 25 mM Pipes buffer, pH 6.5) at 65°C for 40 hours with 25 µg of mRNA extracted from human fibroblasts which had not been induced by poly(I)(C) by the same method as to extract poly(I)(C)-induced mRNA. The reaction mixture was put on a hydroxyapatite column, and elution is first carried out with 0.14 M phosphate buffer (pH 6.5) to eluate the single-straded DNA, and then with 0.4 M phosphate buffer to eluate the DNA hybridized with RNA. As the result, the DNA (about 90 % of the whole) (Probe A) which hybridized with the mRNA mentioned above, and the DNA (about 10 % of the whole) (Probe B) which did not hybridize with it were isolated.

Each probe was hybridized with the above DNA fixed on the nitrocellulose filter according to the Grunstein-Hogness method. By means of autoradiography four strains were isolated which react mainly to Probe B but

little to Probe A.

Table 2 shows the extent of reaction of the DNAs from the four strains to each probe as revealed by autoradiogram.

Table 2

Ampicillin-resistant strains	Extent of Reaction of Probe with DNA in the strains	
	Probe A	Probe B
# 319	+ +	+ + + +
# 644	+	+ + +
# 746	-	+ +
#3578	+	+ + + + +

Plasmid DNA was isolated from cells of the four strains by the method of Currier and Nester [Analyt. Biochem. vol. 76, p.431-441 (1976)]. Then, these DNAs were hybridized with the interferon mRNA as follows;

First, 5 µg of plasmid DNA was incubated with restriction endonuclease Hind III which can be obtained from Haemophilus influenzae Rd in 50 µl of a reaction mixture (10 mM Tris-HCl, pH 7.5; 6 mM $MgCl_2$; 50 mM NaCl; 6 mM mercaptoethanol; 5 units Hind III) at 37°C for 2 hours and thus cut with the restriction endonuclease. After deproteinization with phenol, the cut DNA was precipitated with ethanol and dissolved in 20 µl of 80 % (w/v) formamide. The solution was heat-denatured at 85°C for 10 minutes and was incubated in the solution consisting of 2.5 µg mRNA, 20 µl 80 % (w/v) formamide, 20 mM Pipes buffer (pH 6.5), 0.4 M NaCl and 5 mM EDTA, at 53°C. Four hours later the mixture was mixed with 0.4 ml of 3 x SSC (1 x SSC corresponds to 0.15 M NaCl, 0.015 M sodium citrate) at 0°C, and was filtered through a nitrocellulose filter (diameter : 1 cm, pore size : 0.45 µm) at a rate of about 0.5 ml per minute. After washing the filter with about 1.5 ml of 2 x SSC, the filter was immersed in a solution consisting of 0.6 ml of 90 % (v/v) formamide, 20 mM Pipes buffer, 0.1 %

SDS (sodium dodecylsulfate) and 5 mM EDTA. The incubation of the filter at 60°C for 2 minutes and the removal of the solution were repeated 3 times and the RNA eluted from the nitrocellulose filter into the solution (1.8 ml) was precipitated with ethanol. mRNA containing poly(A) was isolated from the RNA by using oligo(dT) cellulose column chromatography, dissolved in a mixture of 3 µl of 10 mM Tris-HCl (pH 7.5) and 88 mM NaCl and injected into the oocytes of African claw toad. The interferon activity (antiviral activity) in the synthesized protein was determined.

Table 3 shows the interferon mRNA activity of the mRNA which has hybridized with the DNA derived from the four bacterial strains mentioned above.

Table 3

Bacterial strain	Interferon mRNA activity (unit/ml)
# 319	360
# 644	< 10
# 746	15
#3578	< 10
pBR322DNA	< 10

Further experiment was carried out using strain #319 DNA.

5 µg of plasmid DNA obtained from strain #319 by the Currier and Nester method was cut with restriction endonuclease Hind III in the same way as mentioned above. The DNA and the recombinant plasmid βGpBR322 DNA (the vector was pBR322) (obtained from the Institute for Molecular Biology I of University of Zürich) containing rabbit β-globin gene, separately or as a mixture, were hybridized with the mixture of rabbit globin mRNA (obtained from rabbit red blood cells) (1 µg) and interferon mRNA (2.5 µg) obtained from human fibroblasts under the same conditions as mentioned above. The mRNA which formed hybrid was injected into the oocytes of an African claw toad.

The oocytes were incubated for 15 hours in Barth's culture medium containing [^{3}H] labelled histidine and [^{3}H] labelled globin was isolated by acrylamide gel electrophoresis and determined quantitatively by fluorography. The interferon was determined by antiviral activity as described above. The synthesis of rabbit β-globin and the human interferon was determined in this way. The result is shown in Table 4.

Table 4

D N A	Synthesized interferon activity	Amount of globin synthesized
# 319	200 (units/ml)	-
βGpBR322	35	+ + + +
mixture of both plasmids	160	+ + +

From the result of this experiment it has been proved that DNA of #319 has DNA (the interferon gene) which forms a hybrid specifically with the interferon mRNA.

The DNA of #319 was cut with several restriction endonucleases and a restriction endonuclease map [Fig. 1(a)] was made by agalose electrophoresis. Fig. 1 illustrates restriction endonuclease maps of a gene which shows complementarity to the human fibroblast interferon mRNA in the recombinant #319 used to make a novel recombinant plasmid #319-13 and a gene which shows complementarity to the human fibroblast interferon mRNA in the novel recombinant plasmid #319-13.

Restriction endonucleases, Pst I, Bgl II and Hind III (sold by Bethesda Research Laboratories, USA, etc.) cut #319 DNA at the sites illustrated in Fig. 1 (a).

The segments obtained by cutting #319 DNA with restriction endonucleases Pst I and Bgl II were isolated and purified by gel electrophoresis according to the method of Tabak & Flavell [Nucleic Acids Research, vol.5, p.2321-2332 (1978)], etc. The segments were labelled with ^{32}P according to the method of Rigby, et al. [J. Mol. Biol.

vol. 113, p.237-251, (1977)] and the labelled segment was used as a probe. Many strains containing a plasmid which shows complementarity to the probe were isolated from the above ampicillin-resistant strains according to the above method of Grunstein & Hogness [Proc. Nat. Acad. Sci. U.S.A, vol.72, p.3961-3965, (1975)], namely, colony hybridization method. Plasmid DNAs were obtained from each of the strains according to the above method of Currier-Nester and the inserted portions thereof were cut with a restriction endonuclease such as Hind III. The cut plasmid DNA segments were compared in the length and the longest plasmid DNA segment was selected. The plasmid was named #319-13.

The restriction endonuclease map of the plasmid is illustrated in Fig. 1(b) which implies that the novel plasmid has an mRNA sequence containing the mRNA sequence of #319. Primary structure (base sequence) of the mRNA sequence inserted in the plasmid of #319-13 was determined by the method of Maxam-Gilbert [Proc. Nat. Acad. Sci. U.S.A. vol.74, p.560-564, (1977)]. The primary structure is given below.

```
          Met Thr Asn Lys Cys Leu Leu Gln Ile Ala Leu Leu Leu Cys Phe Ser Thr Thr Ala Leu Ser Met Ser Tyr
GTC AAC ATG ACC AAC AAG TGT CTC CTC CAA ATT GCT CTC CTG TTG TGC TTC TCC ACT ACA GCT CTT TCC ATG AGC TAC
CAG TTG TAC TGG TTG TTC ACA GAG GAG GTT TAA CGA GAG GAC AAC ACG AAG AGG TGA TGT CGA GAA AGG TAC TCG ATG

Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu
AAC TTG CTT GGA TTC CTA CAA AGA AGC AGC AAT TTT CAG TGT CAG AAG CTC CTG TGG CAA TTG AAT GGG AGG CTT GAA
TTG AAC GAA CCT AAG GAT GTT TCT TCG TCG TTA AAA GTC ACA GTC TTC GAG GAC ACC GTT AAC TTA CCC TCC GAA CTT

Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala
TAT TGC CTC AAG GAC AGG ATG AAC TTT GAC ATC CCT GAG GAG ATT AAG CAG CTG CAG CAG TTC CAG AAG GAG GAC GCC
ATA ACG GAG TTC CTG TCC TAC TTG AAA CTG TAG GGA CTC CTC TAA TTC GTC GAC GTG GTC AAG GTC TTC CTC CTG CGG

Ala Leu Thr Ile Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn Glu
GCA TTG ACC ATC TAT GAG ATG CTC CAG AAC ATC TTT GCT ATT TTC AGA CAA GAT TCA TCT AGC ACT GGC TGG AAT GAG
CGT AAC TGG TAG ATA CTC TAC GAG GTC TTG TAG AAA CGA TAA AAG TCT GTT CTA AGT AGA TCG TGA CCG ACC TTA CTC

Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu
ACT ATT GTT GAG AAC CTC CTG GCT AAT GTC TAT CAT CAG ATA AAC CAT CTG AAG ACA GTC CTG GAA GAA AAA CTG GAG
TGA TAA CAA CTC TTG GAG GAC CGA TTA CAG ATA GTA GTC TAT TTG GTA GAC TTC TGT CAG GAC CTT CTT TTT GAC CTC

Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu
AAA GAA GAT TTC ACC AGG GGA AAA CTC ATG AGC AGT CTG CAC CTG AAA AGA TAT TAT GGG AGG ATT CTG CAT TAC CTG
TTT CTT CTA AAG TGG TCC CCT TTT GAG TAC TCG TCA GAC GTG GAC TTT TCT ATA ATA CCC TCC TAA GAC GTA ATG GAC

Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg
AAG GCC AAG GAG TAC AGT CAC TGT GCC TGG ACC ATA GTC AGA GTG GAA ATC CTA AGG AAC TTT TAC TTC ATT AAC AGA
TTC CGG TTC CTC ATG TCA GTG ACA CGG ACC TGG TAT CAG TCT CAC CTT TAG GAT TCC TTG AAA ATG AAG TAA TTG TCT

Leu Thr Gly Tyr Leu Arg Asn Ter
CTT ACA GGT TAC CTC CGA AAC TGA AGA TCT CCT AGC CTG TGC CTC TGG GAC TGG ACA ATT GCT TCA AGC ATT CTT GAA
GAA TGT CCA AGT GAG CGT TTG ACT TCT AGA GGA TCG GAC ACG GAG ACC CTG ACC TGT TAA CGA AGT TCG TAA GAA GTT


CCA GCA GAT GCT GTT TAA GTG ACT GAT GGC TAA TGT ACT GCA TAT GAA AGG ACA CTA GAA GAT TTT GAA ATT TTT ATT
GGT CGT CTA CGA CAA ATT CAC TGA CTA CCG ATT ACA TGA CGT ATA CTT TCC AGT GAT CTT CTA AAA CTT TAA AAA TAA

AAA TTA TGA GTT ATT TTT ATT TAT TTA AAT TTT ATT TTG GAA AAT AAA TTA TTT TTG GTG CAA AAG TCA AAA ...
TTT AAT ACT CAA TAA AAA TAA ATA AAT TTA AAA TAA AAC CTT TTA TTT AAT AAA AAC CAC GTT TTC AGT TTT ...
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It is important that in the sequence there exist without any errors the base sequence [three base pairs] corresponding to the amino acid sequence from the amino-terminal to 13th amino acid of the human fibroblast interferon reported by Knight, et al. [Science vol.207, p.525-526, (1980)]. The fact proves that #319-13 plasmid has the human fibroblast interferon mRNA sequence.
Further, it is apparent from the data of the primary sequence that the plasmid encompasses the entire coding region of the protein of the above mRNA and probably the coding region of the signal peptide.

The supports that transformation of the plasmid or mRNA inserted therein to other expression plasmids enables a host such as Escherichia coli to produce interferon.

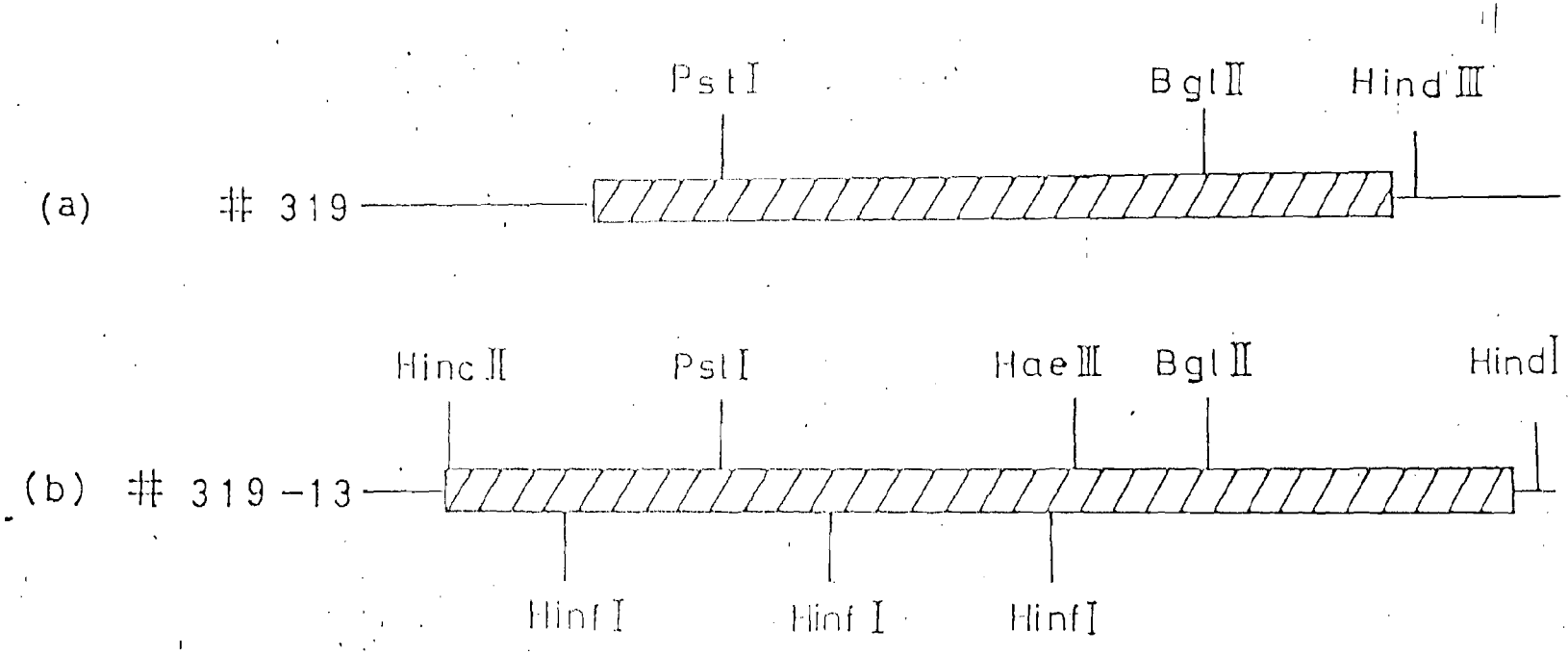
4. Brief Description of the Drawing

Fig. 1 illustrates restriction endonuclease maps of a gene which shows complementarity to the human fibroblast interferon mRNA in the recombinant #319 used to make a novel recombinant plasmid #319-13 and a gene which shows complementarity to the human fibroblast interferon mRNA in the novel recombinant plasmid #319-13.

Applicant: Juridical Foundation,
Japanese Foundation for Cancer Research

Attorney: Junichi Sakata, Patent Lawyer

Fig. 1



Final Hearing
January 17, 1990

Paper No. 270
RHS/raj

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

NTL
5.3400

Patent Interference No. 101,096

Fiers v. Sugano et al v. Revel et al

Production of Interferon

Application of Walter C. Fiers, Serial No. 06/250,609, filed 04/03/81. Accorded benefit of Serial Nos. U.K. 80.11306, filed 04/03/80 and 80.18701, filed 06/06/80.

Application of Haruo Sugano, Masami Muramatsu and Tadatsugu Taniguchi, Serial No. 06/201,359, filed 10/27/80. Accorded benefit of Japanese application 33931/1980, filed 03/19/80.

Application of Michel Revel and Pierre Tiollais, Serial No. 06/425,934, filed 09/28/82. Accorded benefit of Serial No. U.S. 06/208,925, filed 11/20/80 and Israeli application 58765, filed 11/21/79.

James F. Haley, Jr., for Fiers. Oral argument by James F. Haley, Jr.

Joseph M. Fitzpatrick, John Thomas Cella, Lawrence F. Scinto, Carroll G. Harper, William J. Brunet, Robert L. Baechtold, John A. O'Brien, Nels T. Lippert, John A. Krause, Peter Saxon, Henry J. Renk, Anthony M. Zupcic, Charles P. Baker, Edward E. Vassallo, Warren L. Franz and Frederick J. Dorchak for Sugano et al. Oral argument by Nels T. Lippert.

Alvin Browdy, Sheridan Neimark, Roger L. Browdy and James R. Gaffey for Revel et al. Oral argument by Roger L. Browdy.

Interference No. 101,096

R. Smith, Goolkasian and Downey, Examiners-in-Chief.

R. Smith, Examiner-in-Chief.

This interference involves an application of Fiers, Serial No. 250,609, filed April 3, 1981, an application of Sugano et al. (Sugano), Serial No. 201,359, filed October 27, 1980, and an application of Revel et al. (Revel), Serial No. 425,934, filed September 28, 1982 and assigned to Yeda Research and Dev. Co. LTD, Intstitut Pasteur. The Fiers and Sugano applications are unassigned according to Patent and Trademark Office records. 37 CFR 1.201(c).

The subject matter at issue relates to a DNA which leads to the production of human fibroblast interferon-beta, a naturally occurring protein useful in the treatment of viral diseases. The sole count at issue, count 2, corresponds exactly to claim 28 of Revel. Claim 31 of Fiers and claim 40 of Sugano correspond substantially to count 2, which reads as follows:

Count 2

A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

The interference was declared on August 30, 1983 and is therefore governed by the "old" interference rules, 37 CFR 1.201-1.288. All three parties filed briefs and appeared, through

counsel, at final hearing for oral argument. No issue of interference-in-fact was raised by the parties in their briefs at final hearing.

The interference is among three foreign inventive entities, with each party claiming benefit of one or more foreign priority applications under 35 USC 119. Additionally, Fiers presented evidence of conception in this country coupled with evidence relating to diligence toward his constructive reduction to practice. The issue for our determination is priority of invention.

Fiers Motion for Return of Fiers' Papers Filed under Seal

In an unopposed motion Fiers requests that the sealed envelopes containing twelve pages of testimony (pages 337-343 and 571-580) and unredacted exhibits 4, 7 and 8 be returned to Fiers' counsel. Fiers notes that no party has relied on the Fiers' materials filed under seal. The motion is granted. Accordingly, the sealed envelopes are hereby returned to Fiers with this decision.

Fiers' Case for Priority

Fiers, as the junior party to this interference, has the burden of proving prior invention by a preponderance of the evidence. Peeler v. Miller, 535 F.2d 647, 190 USPQ 117 (CCPA 1976). During the motion period of the interference, Fiers moved for benefit of his April 3, 1980 and June 6, 1980 British filing

dates. His motion was not opposed by either Sugano or Revel and was granted by the primary examiner in his Decision on Motions (Paper No. 76) and in his Supplemental Decision on Motions (Paper No. 101). Neither Sugano nor Revel is entitled to challenge Fiers' entitlement to his April 3, 1980 British filing date because neither Sugano nor Revel opposed the Fiers' motion for benefit. Thus, Fiers urges that in the event that the Board of Patent Appeals and Interferences (Board) finds that neither Sugano nor Revel is entitled to his foreign filing date, then Fiers would be entitled to an award of priority of invention because his April 3, 1980 British filing date is prior to the US filing dates of Sugano and Revel.

In the event the Board holds that Sugano or Revel is entitled to the benefit of a foreign application, Fiers urges that his evidence is sufficient to establish conception in this country before any filing date that Sugano or Revel can claim. Further, Fiers presented evidence of reasonable diligence from a time prior to the foreign application dates of Sugano and Revel until the constructive reduction to practice on April 3, 1980 when Fiers filed his British application. The evidentiary record relied on by Fiers includes the declaration testimony of inventor

Fiers and of corroborating witnesses Haley, Gilbert, Sharp, Lawrason and Bailey, associated exhibits and two printed publications.[1]

On September 21, 1979 Fiers made a presentation to the Biogen Scientific Board at a meeting in Paris. He presented his protocols and his actual progress to date toward isolating and identifying a DNA coding for human fibroblast interferon-beta (Fiers Record (FR) 3-5, 345-348). Both Dr. Sharp and Dr. Gilbert were present at the meeting in Paris, and both presented opinion testimony that "one of ordinary skill in the art would have been able to carry out those steps [presented by Fiers] without undue experimentation to produce a DNA which coded for a human fibroblast interferon-beta polypeptide" (FR 348, 501). Fiers urges that the evidence is sufficient to establish conception in the United States as of September 23, 1979 when Dr. Sharp returned to the United States or on September 24, 1979 when Dr. Gilbert returned to the United States.

On January 12, 1980 Fiers made a second presentation to Biogen's Scientific Board in Martinique (FR 348-350, 501-503). Both Gilbert and Sharp were present, both returned to the United

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[1]Pursuant to a stipulation among the parties, "new" rules 37 CFR 1.653 and 1.671 through 1.685 governed the taking of testimony even though the interference was declared under the "old" rules.

States on January 15 and 17, respectively, and both testified that on the basis of Fiers' disclosures "one of ordinary skill in the art would have been able to carry out those steps without undue experimentation to identify a DNA that coded for a human fibroblast interferon" (FR 350, 502). Fiers urges that the evidence of the January, 1980 activity establishes conception of the invention of the count by January 15, 1980. Further, Fiers urges that a draft patent application brought back into the United States on February 26, 1980 is further evidence of conception by that date.

Fiers made a third disclosure to Biogen's Scientific Board on March 28, 1980 in Switzerland when he reported that he had successfully determined the entire nucleic acid sequence of a DNA coding for human interferon-beta and described a protocol to prepare that complete DNA. Fiers disclosed by telephone to Haley in New York on March 25, 1980 that he had determined the DNA nucleotide sequence of several clones and had been able to reconstruct the complete sequence from two of those clones (FR 13, 173). From March 31 until April 2 Fiers and his attorney Haley worked in Ghent drafting the final portion and claims of the Fiers patent application, which was filed in the British Patent Office on April 3, 1980.

Opinion re Fiers' Case for Priority

We hold that Fiers is entitled to the April 3, 1980 British filing date as a constructive reduction to practice of the invention of the count. As noted by Fiers, neither Sugano nor Revel opposed his motion for benefit, which was granted by the primary examiner. Sugano's argument in his brief that Fiers is not entitled to the benefit of the April 3, 1980 filing date is plainly belated and is entitled to no consideration. Magdo v. Kooi, 699 F.2d 1325, 1329-30, 216 USPQ 1033, 1037 (Fed. Cir. 1983).

We further hold that Fiers has failed to establish by a preponderance of the evidence conception in the United States at any time prior to his April 3, 1980 British filing date. Accordingly, Fiers' case for prior conception coupled with reasonable diligence from prior to his opponent's foreign filing dates until his constructive reduction to practice on April 3, 1980 has not been established. Fiers cannot prevail in this interference unless the Board finds that neither Sugano nor Revel is entitled to the benefit of a foreign application.

Conception is the "formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." Hybritech Inc. v. Monoclonal Antibodies, Inc., 802

F.2d 1367, 1376, 231 USPQ 81, 87 (Fed. Cir. 1986). Conception requires both the idea of the invention's structure and possession of an operative method of making it. Oka v. Youssefyeh, 849 F.2d 581, 583, 7 USPQ2d 1169, 1171 (Fed. Cir. 1988).

The invention of the count at issue is a DNA "which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide." Prior to late in March, 1980 the structure of this DNA was unknown to Fiers, and there is no evidence that Fiers introduced the sequence of this DNA into the United States prior to his April 3, 1980 British filing date. A gene or DNA sequence is a chemical compound, albeit a complex one, and it is well established that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. When an inventor is unable to envision the detailed chemical structure of the gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the gene has been isolated. Amgen, Inc. v. Chugai Pharmaceutical, Inc., 18 USPQ2d 1016 (Fed. Cir. 1991). It is not sufficient to define the gene by its principal biological property, e.g., encoding for fibroblast interferon-beta, "because

an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Amgen, Inc., supra.

Although Fiers has presented opinion testimony of two experts who believe that Fiers' disclosures in September, 1979 and January, 1980 would have enabled one of ordinary skill in the art to produce a DNA which codes for human fibroblast interferon-beta, success was not assured or certain until the gene was in fact isolated and its sequence known. This is confirmed by the testimony of Fiers and his attorney Haley who decided not to file a patent application until the sequence was in hand or the expression achieved (FR 7, 162). Fiers testified at page 7 that it was his scientific opinion that until he could show that a selected cDNA either actually expressed fibroblast interferon or coded for an amino acid sequence that corresponded to the partial sequence known for native fibroblast interferon, "I could not state with any certainty that my selected sequence coded for a fibroblast interferon polypeptide." Only after Fiers had identified clones having the complete sequence coding for fibroblast interferon and demonstrated that such sequence corresponded to the partial amino acid sequence reported for native fibroblast interferon was the patent application completed and filed on April 3, 1980 (FR 15).

Sugano's Case for Priority

During the motion period, Sugano moved for benefit of the October 30, 1979 filing date of Japanese Application 139289/79 and the March 19, 1980 filing date of Japanese Application 33931/80. The primary examiner granted Sugano's motion for benefit of the March 19, 1980 Japanese filing date but denied benefit of the October 30, 1979 Japanese filing date. In his decision the primary examiner pointed out that Strain #319 of the 1979 Japanese application does not contain a disclosure for a complete gene for human fibroblast B1 interferon while Strain #319-13 of the March 1980 Japanese application does contain a disclosure for a complete gene for human fibroblast B1 interferon. The primary examiner further held that where the exact DNA sequence for human fibroblast B1 interferon is disclosed, as in the March 1980 application, the disclosure is enabling without a culture deposit.

Fiers urges in his brief at final hearing that Sugano is not entitled to either of his Japanese filing dates. Fiers contends that the burden of proving entitlement to a foreign filing date is on the party seeking benefit, citing Utter v. Hiraga, 845 F.2d 993, 998, 6 USPQ2d 1709, 1713 (Fed. Cir. 1988). Fiers notes that the Sugano 1979 Japanese application fails to describe the subject matter of the count, i.e., a complete DNA

that codes for human fibroblast interferon-beta. With respect to the 1980 Sugano Japanese application, Fiers argues that the application is not enabling even though the full sequence of a DNA that codes for interferon-beta polypeptide is described.

Opinion re Sugano's Case for Priority

We hold that Sugano is entitled to the March 19, 1980 Japanese filing date as a constructive reduction to practice of the invention of the count. We further hold that Sugano is not entitled to the October 30, 1979 Japanese filing date as a constructive reduction to practice of the invention of the count.

The primary examiner found that Sugano met his burden to establish his entitlement to the March 19, 1980 filing date of his Japanese application. We agree with the primary examiner's decision that Sugano has met his burden to establish his entitlement to the March 19, 1980 Japanese filing date. We have reviewed the disclosure of the Japanese application filed March 19, 1980 and we find therein a detailed disclosure of the method used by Sugano to isolate the plasmid DNA segment named Strain #319-13. The application discloses the complete sequence of Strain #319-13, the gene which codes for human fibroblast interferon-beta, and there is no dispute as to the correctness of the sequence disclosed by Sugano's March, 1980 application. Our decision that Sugano has met his burden to establish his

entitlement to his March 19, 1980 Japanese filing date is buttressed by the fact that there is no evidence in the record that would support a contrary finding. Rather, Fiers relies solely on attorney argument in an effort to persuade the Board that the Sugano 1980 application is not enabling. The attorney argument presented by Fiers is unsupported by competent evidence, entitled to little or no weight and is unpersuasive in any event.

Revel's Case for Priority

The primary examiner granted Revel's motion for benefit of his November 21, 1979 filing date of Israeli application 58765 in his supplemental decision on motions (Paper No. 101). In his decision the primary examiner stated that "[i]n the Examiner's view the requirements of 35 USC 119 are met with respect to substituted count 2." Both Fiers and Sugano opposed Revel's motion for benefit, and both urge in their briefs at final hearing that the primary examiner's decision was in error. Revel urges in his brief that once the primary examiner has ruled that Revel is entitled to benefit, the burden is on Fiers and Sugano to establish that the primary examiner's decision was in error.

Revel contends that his Israeli application is in full compliance with the requirements of the first paragraph of 35 USC 112 insofar as support for the subject matter of count 2 is

concerned. Revel relies on the language on page 7, lines 21-26 of the Israeli application which reads as follows:

> The invention thus concerns also said purified m-RNA (single-stranded or double stranded which can be obtained from the single-stranded one by aid of any suitable polymerase) which comprises normally up to 900-1000 nucleotides. In the same manner it also concerns the corresponding c-DNA which can be obtained by transcription of said RNAs. [Emphasis added]

Opinion re Revel's Case for Priority

We hold that Revel is not entitled to the benefit of his November 21, 1979 Israeli filing date as a constructive reductive reduction to practice of the invention of the count. We agree with Sugano and with Fiers that the primary examiner's decision according such benefit to Revel was in error.

As noted by Fiers and by Sugano, the Revel Israeli application does not contain a written description of a DNA coding for beta-interferon, i.e., there is no sequencing disclosed, nor does the application disclose an intact complete gene. As pointed out by the Court in Amgen, Inc., supra, when the researcher does not know the sequence of a gene, he does not achieve conception of that gene until he reduces it to practice--i.e., until he isolates it--and then conception and reduction to practice occur simultaneously. Logically, one cannot reduce to practice or enable an invention that has not been conceived. Accordingly, it is our view that the filing of the Israeli

application does not constitute a constructive reduction to practice of the invention of the count because Revel did not know at the time the structure of the gene, which had not been isolated.

The Interference Count

In his brief at final hearing Fiers requests that the Board recommend pursuant to 37 CFR 1.259 that the interference be reformed to limit it "to the patentably distinct DNA coding for human fibroblast interferon-beta (or "ß-1" interferon)." However, we find the issue of whether the present count contains patentably distinct species, i.e., ß-1 and ß-2 interferon, is moot in view of our decisions, supra, which result in priority of invention for Sugano, whose claims and proofs are limited to ß-1 interferon. Accordingly, we decline to exercise our discretion to recommend to the Commissioner that the interference be reformed as requested by Fiers. Further, the Revel motion to suppress evidence is dismissed as moot since we found it unnecessary to rely on the testimony alleged to be inadmissable in reaching our decision.

Decision

For the foregoing reasons, priority of invention is hereby awarded to Haruo Sugano, Masami Muramatsu and Tadatsugu Taniguchi, the senior party.

Ronald H. Smith
Examiner-in-Chief

John T. Goolkasian
Examiner-in-Chief

Mary F. Downey
Examiner-in-Chief

BOARD OF PATENT APPEALS AND INTERFERENCES